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STUDIES IN RESPIRATORY AIR FLOW

III. The Mechanics of Respiration in the Dog as Reflected by Changes in Intraperitoneal Pressure*

ALAN C. WOODS, Jr., DONALD F. PROCTOR, JAMES P. ISAACS, and B. NOLAND CARTER II

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Received for publication November 17, 1950

This investigation was undertaken in connection with studies of the forces involved in respiration (1, 2). An incidental, and hitherto unreported, observation led to a series of experiments designed to explore the use of recordings of intraperitoneal pressure for further elucidation of the significance of the pneumotachogram.

It had been previously hypothesized that the inspiratory phase of the pneumotachogram might represent an initial diaphragmatic effort followed by more slowly developing intercostal activity. The experiments reported herein indicate that this hypothesis is incorrect and provide information which substantiates a different interpretation of this phase of respiratory air flow.

Recognition of the fact that the intraperitoneal pressure varied with the different stages of respiration was reported as early as 1863 when Marey (3) stated that the pressure changes produced by respiration in the abdomen were the inverse of those in the thorax. A survey of the literature reveals that in general two methods have been used to estimate the intraperitoneal pressure. In the early studies the pressure within a hollow viscus was measured. Variations in this pressure were assumed to be the effects of (1) changes in intraperitoneal pressure (2) changes in muscle tone within the viscus itself or (3) the hydrostatic changes occurring within the abdominal cavity. Braune in 1865 measured the intrarectal pressure, Schatz in 1872 measured intrauterine pressure, Odebrecht in 1875 measured the pressure in the urinary bladder, and Rosenthal in 1882 measured the intragastric pressure. In

* This work was supported by Grants In Aid from the U. S. Public Health Service.

more recent years variations of this method have been reported by Rushmer (4), Duomarco and Rimini (5), and Mills (6).

The direct method of measurement of the intraperitoneal pressure by means of a trocar or cannula introduced into the intraperitoneal space was used by Keppich (7), Wildegans (8), Wagoner (9), and Overholt (10). A variation of this method was described in 1939 by Lam (11) who introduced a small balloon containing air or fluid into the intraperitoneal space and connected this to a manometer. The papers of Emerson (12), Overholt (10), Rushmer (4), and Lam (11) summarize the methods previously employed.

The results of these investigations have led to the generally accepted belief that intraperitoneal pressure fluctuations are small and that there is a simple rise and fall of the pressure coincident with inspiration and expiration respectively. Banyai (13) has pointed out that expansion of the chest results in an enlargement of the abdominal volume, and states that fluctuations in intraperitoneal pressure are usually in the same direction as changes in intrapleural pressure during pneumoperitoneum.

METHOD

Twenty-two experiments have been carried out on 16 dogs. The animals were anaesthetized with intravenous sodium pentobarbital, a cuffed endotracheal tube about 12 mms. in diameter was inserted, its balloon inflated, and the distal end of the tube attached to the pneumotachometer (1). A curved needle was introduced into the intrapleural space through a small nick in the skin and muscle. This needle had several side perforations wihtin its concavity to avoid obstruction by lung. A small right rectus incision (usually less than 2 cms. long) was made in the right upper quadrant through which a Foley-type catheter, with numerous side perforations, was introduced, allowing as little air as possible to enter the peritoneal cavity. This catheter was sewn tightly in place to prevent entrance or egress of air, and the balloon was inflated to serve as a cuff within the abdomen, the opening of the catheter lying about 10–15 cms. below the dome of the diaphragm and about 3–5 cms. posterior to the anterior wall. These cannulae were connected to Statham bellows-type strain gauge manometers, the outputs of which were recorded through galvanometers with a natural frequency of about 180 cycles per second. The other aperture of each gauge was open to the atmosphere so that changes in pressure were recorded with reference to atmospheric pressure. The deflections of the galvanometers were recorded on a 6 inch wide strip of photographic paper in the camera of a Hathaway oscillograph. A similar strain gauge and galvanometer was used to record the pneumotachogram.

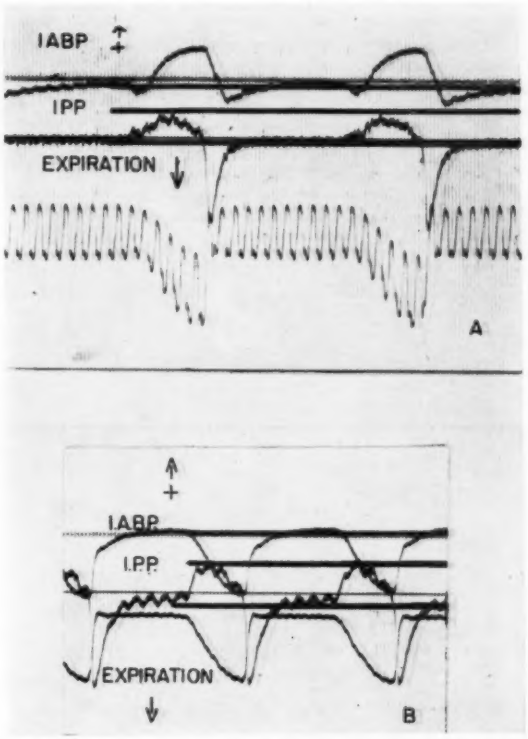

FIG. 1. A. Record from a normal dog. Upper tracing (IABP): intraperitonea pressure; middle tracing: pneumotachogram, lower tracing: intrapleural pressure Zero straight lines represent atmospheric pressure and zero flow velocity. The time lines measure 0.1 seconds. Note the prolonged inspiration at relatively low rates of flow and the sharp peak flow of expiration. The prolonged post-expiratory pause is characteristic of most dogs under pentobarbital anaesthesia. Intraperitoneal pressure becomes negative at the onset of inspiration, then positive, and negative again at the onset of expiration. Intrapleural pressure becomes increasingly more negative as inspiration continues, returning to the base-line shortly after the onset of expiration. The large fluctuations in the intrapleural pressure coincide with the heart beat.

B. Record from the same dog after the phrenic nerves have been severed. Peak flow in the pneumotachogram appears at the onset of inspiration, in contrast to the slow acceleration in figure 1-A; velocity during the latter half of inspiration is relatively low. The curve of the intraperitoneal pressure exactly follows that of intrapleural pressure differing only in the degree of pressure change.

The pneumotachogram, intrapleural pressure, and intraperitoneal pressure thus were recorded simultaneously in normal anaesthetized dogs as well as in dogs with bilateral complete phrenic sections, and dogs with intact phrenic nerves but with the spinal cord completly severed below the seventh cervical segment to paralyse

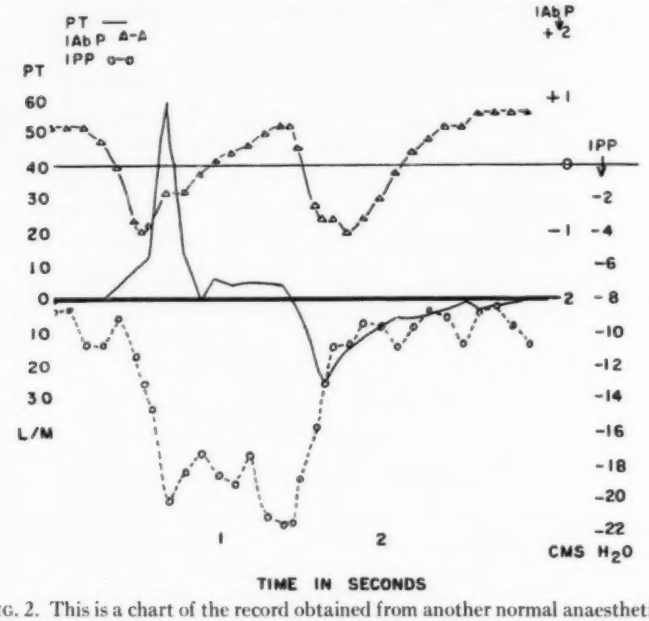

FIG. 2. This is a chart of the record obtained from another normal anaesthetized dog. The figures to the left pertaining to the velocity of air flow in the pneumotachogram, are in liters per minute, the figures to the right refer to pressure in centimeters of water. This animal had an initial inspiratory gasp. The intraperitoneal pressure during the post expiratory pause in this dog in this position is +1 centimeter of water pressure. It drops abruptly with the initial gasp in inspiration, rising to +1 centimeter of water pressure again during the remainder of the inspiration and falls again to a negative pressure with expiration. This seems to be a clear demonstration of inspiratory activity not attributable to diaphragmatic contraction.

the intercostal nerves. Because of the fact that, in the dog, the root of the phrenic nerve from the 5th cervical segment joins the main trunk of the phrenic low in the superior mediastinum the phrenic nerves were severed in the chest by a transpleural approach. Under positive pressure anaesthesia (14) the right chest was

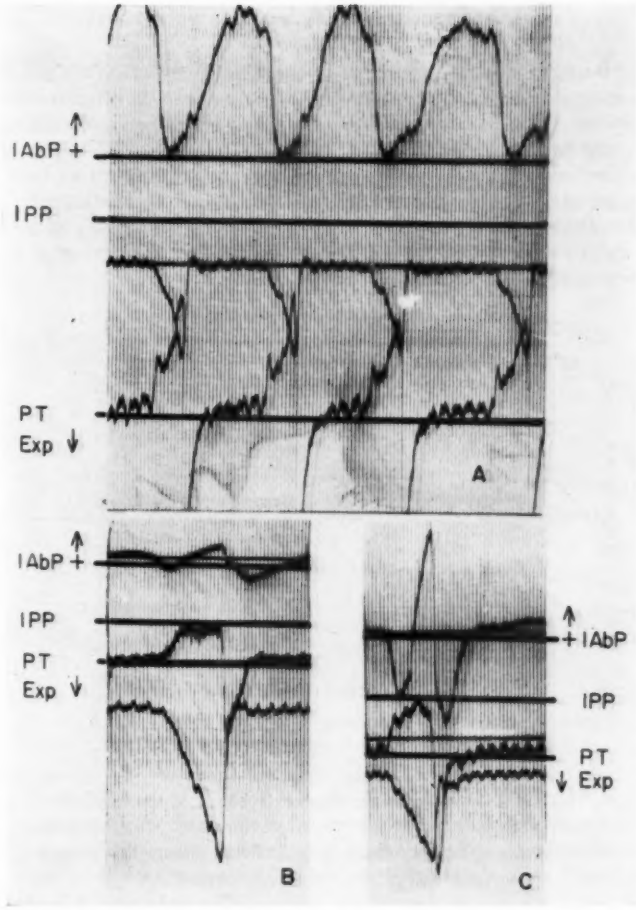

FIG. 3. These records were taken from a normal anaesthetized dog in three different positions, to show the hydrostatic effects of the intraabdominal contents upon the intraperitoneal pressure when it is measured in the epigastrium. Figure 3 A was obtained with the dog in the supine position with the foot of the table elevated 45 degrees. The intraperitoneal pressure is positive in all phases of respiration.

Figure 3 B shows the record obtained when the dog was in the same position with the table level.

Figure 3 C records the pressure when the head end of the table was elevated 45 degrees. Note that the intraperitoneal pressure becomes more deeply negative at the onset of inspiration and in expiration.

opened through a small incision in the anterior third interspace. The right phrenic nerve was picked up with a small hook as it coursed along the superior vena cava and divided. A small incision was then made through the superior thoracic mediastinum, and the left phrenic nerve was picked up and divided. The lungs were then reexpanded under positive pressure, and the chest wall was closed air tight. As a precaution against pneumothorax bilateral thoracenteses were performed.

Subsequent to these experiments fluoroscopic motion pictures of a normal dog's chest (with simultaneous pneumotachogram) were made by members of the Department of Radiology at the University of Rochester.

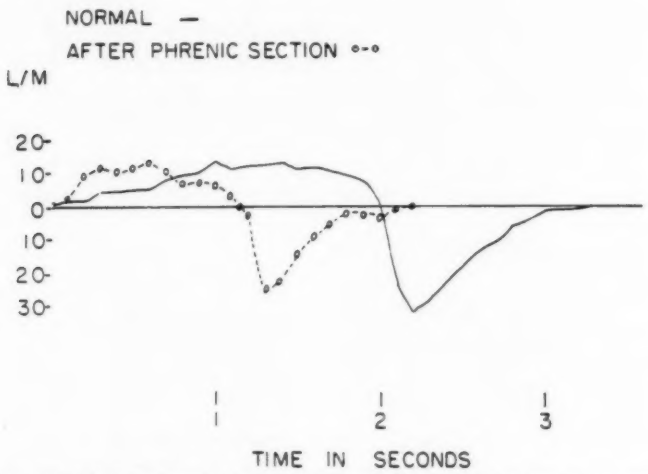

FIG. 4. This figure emphasizes the changes in shape of the inspiratory pattern of the pneumotachogram in the normal dog before and after bilateral phrenic section. After phrenic section note that the peak flow in inspiration is reached much sooner than in the normal dog but is not well maintained.

Records were also obtained on 4 dogs breathing through the mediation of the phrenic respirator of Sarnoff (15).

RESULTS

Intraperitoneal pressure became negative relative to its resting baseline in the first part of the inspiratory phase in 14 of the 16 dogs studied. In 2 dogs the intraperitoneal pressure did not show a negative dip during inspiration. In these dogs when the anterior abdominal wall was raised about 5 centimeters by pulling on the cannula leading into

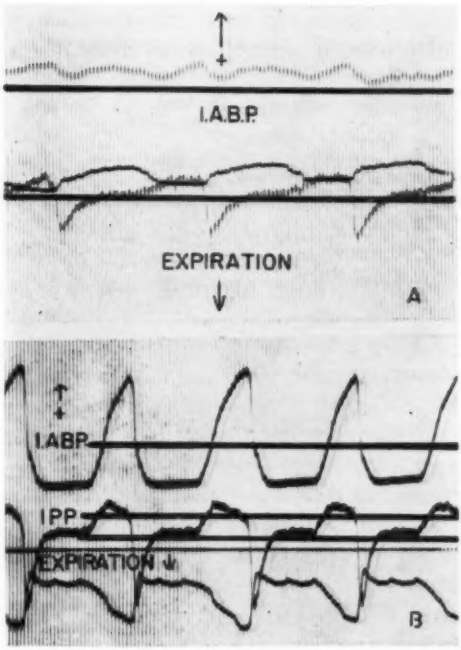

FIG. 5. A. Record from another normal dog. The intraperitoneal pressure (IABP) in this animal is posit ve in all phases. The dicrotic nature of the curve is again apparent. The middle line in this record is to be ignored. The lower line is the pneumotachogram.

B. Record obtained, from the same dog shown in figure 3 A, after section of the spinal cord below the level of C-7. Peak air flow velocity is now reached toward the middle of the inspiratory phase. The intrapleural pressure curve has not changed its general characteristics. The intraperitoneal pressure curve (IABP) moves in the opposite direction from the intrapleural pressure curve, the pressure becoming more positive during inspiration as the diaphragm contracts and descends and as the intrapleural pressure becomes more negative.

the intraperitoneal space the negative dip appeared on the record. The fluctuations in the intraperitoneal pressure seldom exceeded two to four centimeters of water (fig. 1).

In some anaesthetized dogs inspiration consisted of an initial gasp followed by a decrease in flow velocity and a final increase in flow veloc-

ity before expiration began. In those dogs the initial gasp coincided with the negative wave in intraperitoneal pressure (fig. 2).

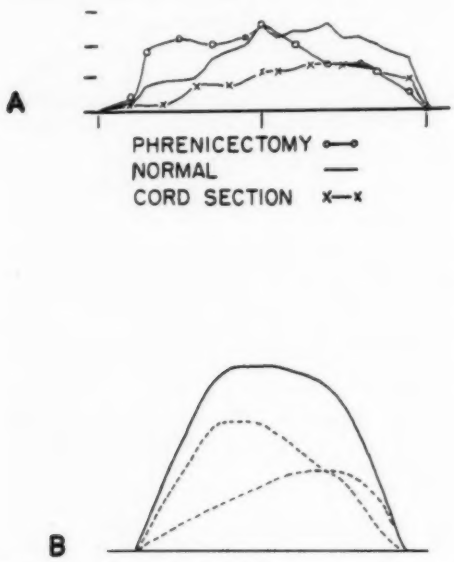

FIG. 6. A. This figure shows three inspiratory curves reduced to the same time base (that is, corrected for the difference in respiratory rates in the three animals from which the curves were taken). The curve after phrenicectomy shows peak inspiratory flow earlier in the cycle than in the normal dog. The curve in the spinal dog shows peak flow late in the inspiratory cycle.

B. The dotted lines in this figure show two theoretical curves of flow velocity which, when summated, combine to produce the curve shown with a solid line. One curve with peak flow early in inspiration, has the general characteristics of intercostal activity alone, as shown in the phrenicectomized animals. The other with a peak flow late in inspiration resembles the inspiratory patterns obtained in spinal animals, where the diaphragms alone expand the lungs. The solid line is taken from an inspiratory pneumotachogram in a normal human.

When the head end of the table (on which the dog was tied supine) was elevated the entire pressure pattern in the upper anterior abdomen became more negative. The reverse was the case when the foot end of the table was elevated (fig. 3). The negative dip in intraperitoneal

pressure at the onset of inspiration was much more pronounced when the head end of the table was elevated. The pneumotachogram remained virtually unchanged in the level and head up positions but in the head down position the much higher flow velocities reflected an increased ventilation.

After section of both phrenic nerves two effects were noted. Intraperitoneal pressure exactly followed, in direction, intrapleural pressure (the former showing smaller changes than the latter) (fig. 1B). The early rise in air flow velocity during inspiration was more marked than in the normal animal but the normal maintenance of relatively high velocity was absent (fig. 4).

When the spinal cord was sectioned below C-7 intraperitoneal pressure became the inverse of intrapleural pressure during inspiration. Under this circumstance the initial rise in inspiratory flow velocity was delayed and the peak flow velocity was relatively late in the phase (fig. 5).

A summation of the inspiratory phase of the pneumotachograms obtained with phrenic paralysis and intercostal paralysis gives a pattern quite similar to the normal inspiratory curve (fig. 6).

Studies of cinefluorographic pictures are not yet complete. So far only lateral views have been taken. From these it is apparent that there is very little alteration in the anterior-posterior diameter of the chest, but what variation there is occurs early in the inspiratory phase. From the lateral view the diaphragm is seen not only to descend but to alter shape during inspiration. Its descent occurs slowly. No actual rise of the diaphragm during inspiration is apparent.

DISCUSSION

The studies of intraperitoneal pressure in normal dogs, those with diaphragmatic paralysis and those with intercostal paralysis demonstrate the following:

1. During inspiration intraperitoneal pressure becomes relatively negative before becoming positive.

2. The shape of the pneumotachogram during inspiration represents mainly intercostal activity during the first few tenths of a second and mainly diaphragmatic activity during the latter part of the inspiratory phase.

Preliminary studies with the Sarnoff phrenic respirator (15) show that descent of the diaphragm and rise in intraperitoneal pressure occurs very rapidly after direct stimulus of the exposed phrenic nerves with this apparatus indicating that there is little delay in contraction

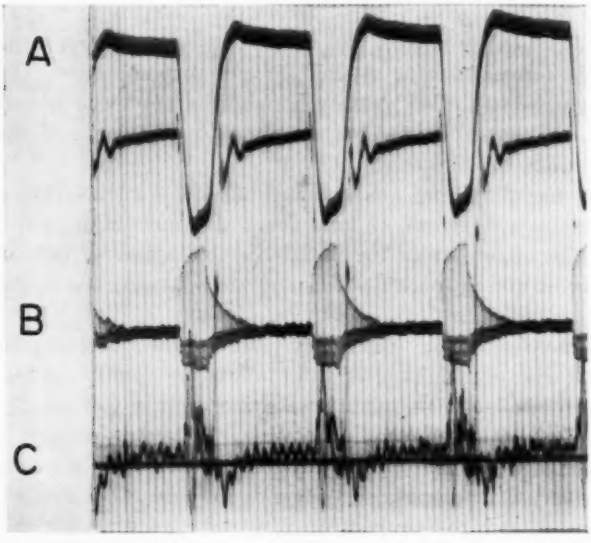

FIG. 7. Record from a normal dog breathing under the mediation of the Sarnoff electrophrenic respirator.

A. Intraperitoneal pressure, movement of the tracing downwards indicates positive pressure.

B. Signal to indicate stimulus of the phrenic nerves with the respirator.

C. Pneumotachogram: inspiration is indicated by movement of the tracing upwards.

The rise in intraperitoneal pressure begins very rapidly after stimulus of the phrenic nerves. Time lines are at one tenth of a second intervals.

of the diaphragm when stimulated in this fashion (fig. 7). The highest point of positive intraperitoneal pressure and the peak velocity of inspiratory air flow is reached in about one tenth of a second after stimulus of the phrenic nerve. The onset of inspiratory air flow and the start of the rise in intraperitoneal pressure occur almost immedi-

ately after stimulus of the nerve, certainly in less than one twentieth of a second.

The decrease in intraperitoneal pressure at the onset of inspiration must be associated with some increase in intraabdominal volume (perhaps an infinitesimally small one). This could be owing to an actual ascent of the diaphragm or to elevation of the abdominal wall due to movement of the rib cage. In any event it seems probable that intercostal activity is effective earlier in the inspiratory cycle than diaphragmatic activity.

The experiments with the electrophrenic respirator indicate that there is little delay in diaphragmatic descent after the phrenic nerve has been stimulated. Sufficient evidence is not yet available to say whether the delayed diaphragmatic descent in normal anaesthetized dogs is attributable to any one of several possible causes. Among these are: 1. Temporal dispersion resulting from either delays arising in the sequence of firing within the central integrating respiratory areas or apparent delay in contraction of the diaphragm produced by the relatively prolonged period of recruitment which characterizes phrenic function. 2. Antagonism between the effects of intercostal and diaphragmatic activity. Larrabee and Hodes (16) demonstrated that as inspiration progresses there is an increasing frequency of impulses passing through the individual fibers. Such a stimulus is possibly somewhat different from the one delivered by the Sarnoff stimulator.

The fact that elevation of the anterior abdominal wall produces the negative pressure dip when it is not ordinarily present is probably attributable to a splinting effect in an abnormally flaccid abdominal wall. The increase in this dip when the head end of the table is elevated is most likely a result of a lowering in the position of the diaphragm due to the weight of the abdominal viscera. When the foot end of the table was elevated the increase in ventilation was in some dogs quite marked and accompanied by indications of general distress. One would wonder if an alteration in the circulation contributed to these changes.

Although the cinefluorographic observations will probably be of greater significance when other views are studied, the evidence obtained from this source so far tends to confirm the relatively slow diaphragmatic descent in comparison to expansion of the chest but

does not demonstrate any actual rise in the diaphragm at the onset of inspiration.

SUMMARY

1. Fluctuations in intraperitoneal pressures observed in anaesthetized dogs range from one to two cms. of water pressure in contrast to intrapleural pressures which range from 12 to 20 cms. of water pressure.

2. The intraperitoneal pressure in most normal dogs shows 2 peaks in the negative direction: an early negative peak attributed to intercostal contraction at the onset of inspiration, a positive pressure peak as the diaphragm contracts and descends, reducing the volume of the abdominal cavity, and a final negative peak as expiration ensues.

3. Intraperitoneal pressure, and, apparently the pneumotachogram, reflect the dynamically changing balance between intercostal and diaphragmatic activity. Contraction of the intercostals lowers intraperitoneal pressure and diaphragmatic contraction raises it.

4. The intercostal muscles and the diaphragm do not act together in inspiration in the time sense. Evidence has been presented which indicates that the early peak flow in inspiration is due to the action of the intercostals and late peak flow is due to the action of the diaphragm.

The authors wish to express their appreciation to Mr. Sydney A. Weinberg, and George H. Ramsey, M.D., of the Department of Radiology, and Arthur B. Otis, M.D., of the Department of Physiology of the University of Rochester School of Medicine, for the cinefluorographic studies carried on at that institution; and to Mary N. Linderman for technical assistance in all of these studies.

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STUDIES ON A PROTEOLYTIC ENZYME IN HUMAN PLASMA

VI. Alterations in Plasma Fibrinogen and Proteolytic Activity in Pneumonia*

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Among the physiologic changes which occur in the human host during infections, one of the most dramatic is the rise in the concentration of fibrinogen in the circulating plasma (1–3). The mechanisms which bring about this change have not been made clear. The rate of destruction of fibrinogen is one possible factor regulating its concentration. Dastre (4) in 1893, observed that plasma contained a proteolytic enzyme system capable of digesting fibrin. Subsequently, it was demonstrated that plasma was also capable of digesting fibrinogen (5). Ordinarily, the proteolytic activity of the plasma is held in check by potent inhibitory substances (6). The extent to which variations in the proteolytic activity of plasma determine its concentration of fibrinogen is not understood.

The present study was undertaken to determine whether the changes in the concentration of fibrinogen in acute infections were associated with changes in the proteolytic activity of the plasma. In order to limit the number of variables the study was limited to patients with uncomplicated acute pneumonia. The results of this investigation indicate that in pneumonia, the spontaneous proteolytic activity of plasma was usually low at a time when the concentration of fibrinogen was high. Late during convalescence, the spontaneous proteolytic activity increased. The potentially available proteolytic activity in plasma was usually low during the acute phase of the pneumonia. It uniformly rose early during convalescence, and reached a peak shortly after the concentration of fibrinogen was maximal. The data suggest that in patients with pneumonia a relationship may exist between the plasma's concentration of fibrinogen and its proteolytic activity.

* These studies were conducted under contract with the Office of Naval Research, United States Navy.

METHODS

Nomenclature: The term *plasma proteolytic enzyme* will be used to designate the substance or substances present in plasma capable of digesting fibrinogen, fibrin and casein *in vitro* at neutral pHs. This term is synonymous with plasmin (7) or fibrinolysin (8). The enzyme is ordinarily present in plasma as an inactive *precursor*. The filterable principle of cultures of hemolytic streptococci which activates the precursor will be called *streptococcal fibrinolysin*. The newer term, *streptokinase*, will be reserved to describe the purified streptococcal product isolated by Christensen (9). *Spontaneous fibrinolysis* will be used to describe the fibrinolysis observed in recalcified plasma clots stored in glass tubes and not to denote an *in vivo* phenomenon. As in previous studies (10), the term enzyme does not imply a purified product or even a single substance.

General Plan of Study: Under aseptic conditions, venous blood was drawn several times weekly from the antecubital vein of human subjects and transferred to 15 ml. centrifuge tubes each containing 0.2 ml. of oxalate mixture for every 5 ml. of blood drawn (11). The subjects were all patients on the wards of the Johns Hopkins Hospital during the winter of 1949–1950. Ten had typical pneumococcal pneumonia. Three of these patients were male, and 7 female. Their ages ranged from 22 to 56 years. Two of the patients were chronic alcoholics and 2 had diabetes mellitus. In 1 patient, pneumococcus type I was grown in cultures of venous blood drawn when she was admitted to the hospital on the eighth day of her illness. All of the patients were treated with penicillin. In 3 of the patients, transient, sterile pleural effusions were observed. Otherwise, all 10 patients made uneventful recoveries. In addition, 2 male patients with primary atypical pneumonia were studied. Both were 56 years of age, and in both, tests for cold agglutinins and agglutinins against streptococcus MG were negative. One of the 2 was treated with aureomycin.

As soon as possible after the blood was drawn, the sedimentation rate and hematocrit were determined. Then the blood was centrifuged at 2,000 rpm in a Sorvall angle centrifuge (rim diameter 10″), and the plasma was separated from the cells. Sufficient plasma was set aside for determination of the clot lysis time. The remainder of the plasma was then stored in lusteroid tubes in a carbon dioxide refrigerator at approximately minus 70°C. When the series of plasmas obtained from a patient was completed, the stored plasmas were thawed simultaneously. The concentration of fibrinogen, potential proteolytic activity and gamma globulin were then determined on the whole series of plasmas at the same time. In this way, it was possible to minimize errors which might have arisen from variations in technique from day to day. The inhibitory activity of plasma against the plasma proteolytic enzyme was also determined, but the results of these studies are not reported here. In several of the patients it was possible to obtain samples of blood several weeks after recovery from the pneumonia. The determinations of fibrinogen, potential proteolytic activity and gamma globulin in these samples were usually not made at the same time as the earlier determinations in the same patients.

Measurement of Plasma Fibrinogen: The concentration of fibrinogen in plasma was determined by a method requiring only 0.5 ml. of plasma. Briefly, a volume of 0.5 ml. of plasma was pipetted into a 50 ml. pyrex centrifuge tube containing 10 ml. of a 0.85 per cent solution of sodium chloride, 0.05 ml. of a solution of thrombin containing 1,000 National Institutes of Health units per ml.,[1] and approximately 0.5 ml. of crushed pyrex glass. The mixture was agitated during clotting. The fibrin strands adhered to the crushed glass as they formed, and were then separated from the supernatant serum by centrifugation. The fibrin was washed twice with 10 ml. portions of the sodium chloride solution. Then the amount of fibrin adherent to the glass was determined by measuring its tyrosine-like activity. The details of this method have been reported separately (12). With this technique, the concentration of fibrinogen in the plasma of normal adults ranged from 164 to 415 mg., averaging 281 mg. per 100 ml.

Measurement of Clot Lysis Time: Using the technique necessary for sterility, 1 ml. of fresh oxalated plasma was pipetted into a Wassermann tube 13 mm. in diameter which contained 0.2 ml. of sterile M/20 calcium chloride solution. Six-tenths ml. of the recalcified plasma were immediately pipetted into a second Wassermann tube. The tubes were then closed with sterile rubber stoppers, incubated at 37°C. and observed daily for clot lysis. The length of time from the formation of the clot until the contents of the tube reliquefied and became clear was recorded as the clot lysis time. Under these conditions, fibrinolysis only rarely occurred in normal subjects before the third day. In most normal subjects, the plasma clot usually lysed within 8 days. However, in a few subjects the clot lysis time was 10 days or longer. Those clots which failed to lyse within 10 days usually did not lyse within the next few weeks. For this reason, the clots were usually discarded after 10 days, and at this time the clot lysis time of the unlysed clots was recorded as 10+ days. The clot lysis times in duplicate tubes rarely differed by more than one day. In Figs. 1 to 8, the clot lysis times which have been recorded represent the average of duplicate determinations.

Measurement of Potentially Available Proteolytic Activity of Plasma: In previous studies, the potentially available proteolytic activity of plasma was determined by separating the euglobulin containing the precursor of the proteolytic enzyme from the rest of the plasma. The precursor was then activated with streptococcal fibrinolysin and its activity measured. However, in preliminary experiments it became evident that the amount of fibrinogen in the precipitate of euglobulin was a function of the concentration of fibrinogen in the plasma. For this reason, in the experiments to be reported, the potentially available proteolytic activity was determined in whole plasma diluted with buffer. The buffer solution consisted of 7.30 gm. of sodium chloride, 2.76 gm. of barbital and 2.06 gm. of sodium barbital, diluted to a volume of 1 liter with distilled water. The buffer, then, was composed of 0.125M sodium chloride buffered by 0.025M barbital at pH 7.5.

[1] Bovine thrombin was obtained through the courtesy of Parke-Davis Company, Detroit.

The enzyme in the diluted plasma was activated by the addition of purified streptokinase dissolved in barbital buffer.[2] This preparation, containing 36 units per microgram (9), was dissolved in buffer in a concentration of 10,000 units per ml. of solution, and was stored in a refrigerator at −10°C. until use. Just before use it was diluted with buffer to a concentration of 1,250 units per ml.

The substrate used was a 0.3 per cent solution of casein (vitamin-test, Lot. No. 17218, General Biochemicals, Inc.). Three grams of casein were dissolved at 56°C. in 900 ml. of water containing 6 ml. of 1 N sodium hydroxide. To this were added 3 ml. of 1 N hydrochloric acid and the volume brought to 1 liter with water. The final solution, then, contained 3 mg. of casein per ml., in 0.003N sodium hydroxide and 0.003N sodium chloride.

The amount of precipitable protein present in the enzyme-substrate mixture was determined turbidimetrically. Two ml. of 12.5 per cent hydrochloric acid and 0.5 ml. of 20 per cent sulfosalicylic acid were added in rapid successsion to a 1 ml. aliquot of the solution to be tested. Maximal turbidity appeared in about 5 minutes, and was read in a cuvette of 8 mm. internal diameter with a Coleman, Jr., spectrophotometer at a wavelength of 420 mμ. With the tube, instrument, and lot of casein used, an optical density of 0.265 was equivalent to a concentration of 1.0 mg. of casein per ml. of enzyme-substrate mixture. At 420 mμ, the degree of turbidity obeyed the Lambert-Beer Law to an optical density of approximately 0.565. When the concentrations of enzyme and substrate which exceeded this density were used, correction was made for the deviation of the optical density from this linear relationship.

To determine the potential proteolytic activity of the plasma, 0.4 ml. of thawed plasma were pipetted into a 150 x 15 mm. pyrex tube which was placed in an ice bath. To this tube were then added 4.0 ml. of casein solution, and 1.0 ml. of streptokinase solution containing 1,250 units per ml. As soon as possible after the streptokinase had been added to the mixture of diluted plasma and casein, a 1 ml. aliquot was removed, and the amount of precipitable protein in this sample determined. At the same time, the remainder of the enzyme-substrate mixture was transferred to a water bath at 37°C. After 30 minutes, the amount of precipitable protein was again determined on a second 1 ml. aliquot.

The proteolytic enzyme of plasma digested the preparation of casein used in direct proportion to the concentration of enzyme until approximately 0.8 mg. of casein per ml. remained. Beyond this point, digestion was not linear. For this reason the activity of the proteolytic enzyme of plasma was expressed in arbitrary digestion units, such that 100 digestion units of enzyme digested 0.50 mg. of casein per ml. of enzyme-substrate mixture in 30 minutes. With the technique described, the least potential proteolytic activity which was measurable with accuracy was 800 units per ml. of plasma. Activities less than this were recorded as 800 units per ml. In normal individuals, the potential proteolytic activity of plasma ranged

[2] Purified streptokinase was obtained through the courtesy of Dr. L. R. Christensen.

from 800 to 2,200 units per ml. It should be emphasized that the potential proteolytic activity was determined in whole plasma. It is therefore apparent that this determination was necessarily made in the presence of any inhibitory substances in plasma against the streptococcal fibrinolysin and against the enzyme itself.

Measurement of Erythrocyte Sedimentation Rate: The sedimentation rate of fresh oxalated whole blood was measured in Wintrobe tubes. The upper level of the column of erythrocytes was recorded after 40 minutes instead of the usual 60 minutes. The erythrocyte sedimentation rate was 7.5 mm. or less in 40 minutes in 10 males, and 17.0 mm. or less in 11 female adults who were presumed to be normal. No correction was made for the patient's hematocrit. The hematocrit was determined simultaneously. In none of the patients was there a significant change in hematocrit during the period of observation.

Measurement of Plasma Gamma Globulin: The concentration of gamma globulin in thawed plasma was measured by the indirect method described by Kunkel, (13), using a dilute buffered solution of zinc sulfate. Since the turbidity developed in plasma varied somewhat from batch to batch of zinc sulfate solution, all the determinations were made with a single batch of reagent. With this reagent, the turbidity of plasma varied from 6 to 18 units in normal individuals.

EXPERIMENTAL

1. *Plasma Fibrinogen in Pneumococcal Pneumonia.*—In each of the patients studied, the concentration of fibrinogen was increased above normal during the acute phase of the pneumonia. The highest concentrations observed were in 2 patients with concomitant diabetes mellitus. These concentrations were 1090 and 1250 mg. per 100 ml. of plasma respectively. In 8 of the patients, the highest level of fibrinogen was observed on the third to tenth day of illness. This peak usually occurred 2 to 3 days after the patient's temperature had begun to fall. In the other 2 patients, the earliest sample tested contained the highest concentration of fibrinogen.

During convalescence, the concentration of fibrinogen in plasma gradually fell, reaching normal levels only after several weeks. Data obtained in 6 of the 10 patients have been charted in Figs. 1–6. The values obtained in the other 4 patients did not differ significantly from these.

The erythrocyte sedimentation rate is said to depend in part upon the concentration of fibrinogen in plasma (14). However, changes in the sedimentation rate cannot always be correlated with changes in the concentration of fibrinogen in plasma (15). In the patients with pneumococcal pneumonia described in the present report, there was

relatively little correlation between the concentration of fibrinogen in plasma and the uncorrected erythrocyte sedimentation rate, measured at 40 minutes.

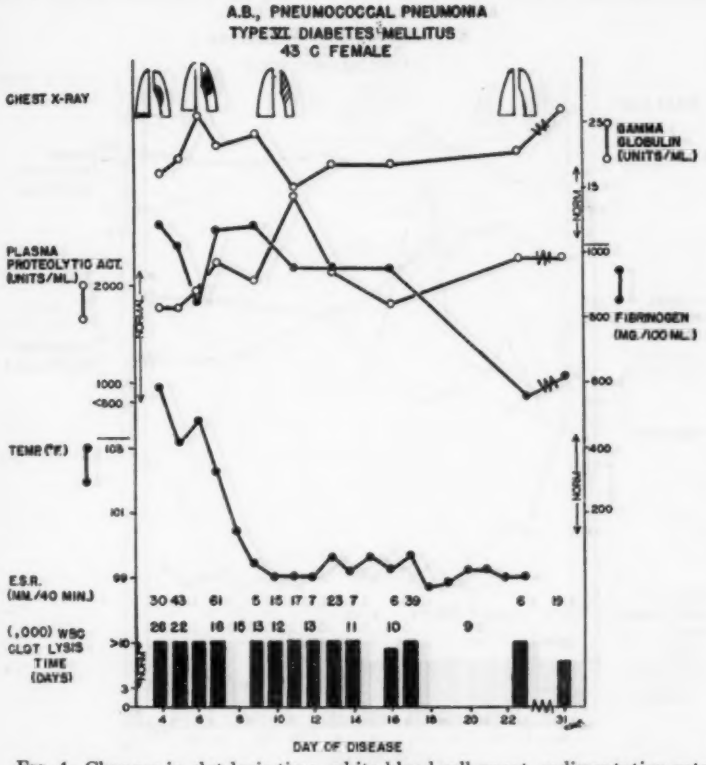

FIG. 1. Changes in clot lysis time, white blood cell count, sedimentation rate, potential plasma proteolytic activity, plasma fibrinogen and plasma gamma globulin in a patient with lobar pneumonia. In this and the succeeding figures, the range of normal is indicated by arrows.

2. *Clot Lysis Time in Pneumococcal Pneumonia.*—During the acute stage of pneumonia, the clot lysis time of recalcified plasma was usually relatively long. In 8 of the 10 patients studied, the clot lysis time was 10 days or longer at a time when the concentration of fibrinogen was

increasing or at its peak. Late during covalescence, the clot lysis time shortened in these 8 patients. It is noteworthy that this increase in fibrinolytic activity *in vitro* usually occurred some days after the concentration of fibrinogen in plasma had begun to decrease (Figs. 1–6).

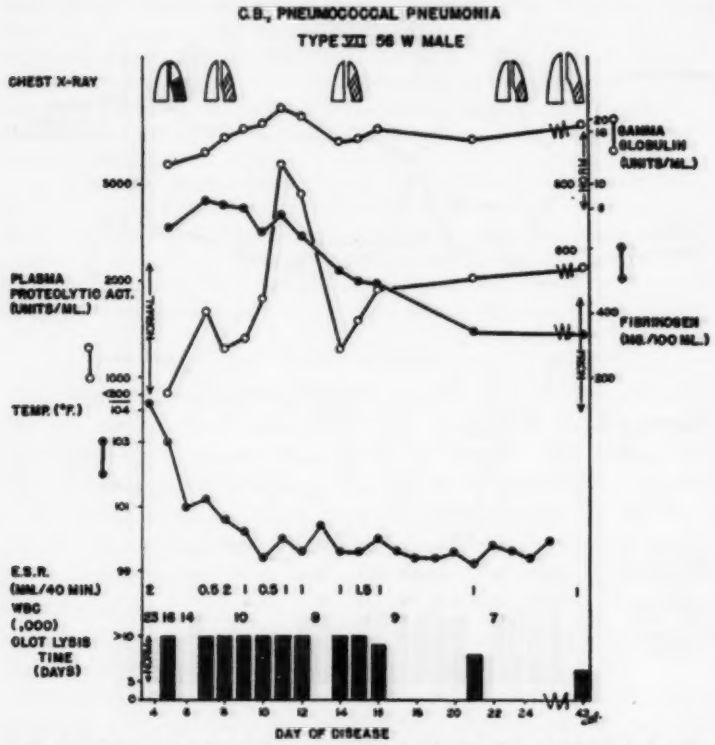

FIG. 2. Changes in clot lysis time, white blood cell count, sedimentation rate, potential plasma proteolytic activity, plasma fibrinogen and plasma gamma globulin in a patient with lobar pneumonia.

3. *Potentially Available Plasma Proteolytic Activity in Pneumonia.*— The most striking change observed in the patients with pneumococcal pneumonia was in the amount of potentially available plasma proteolytic activity. In every patient, this activity increased early during

the course of the pneumonia. In 7 of the patients, it reached a maximum 2 to 7 days after the concentration of fibrinogen was at its highest level. In 2 others, it was maximal in the samples with the

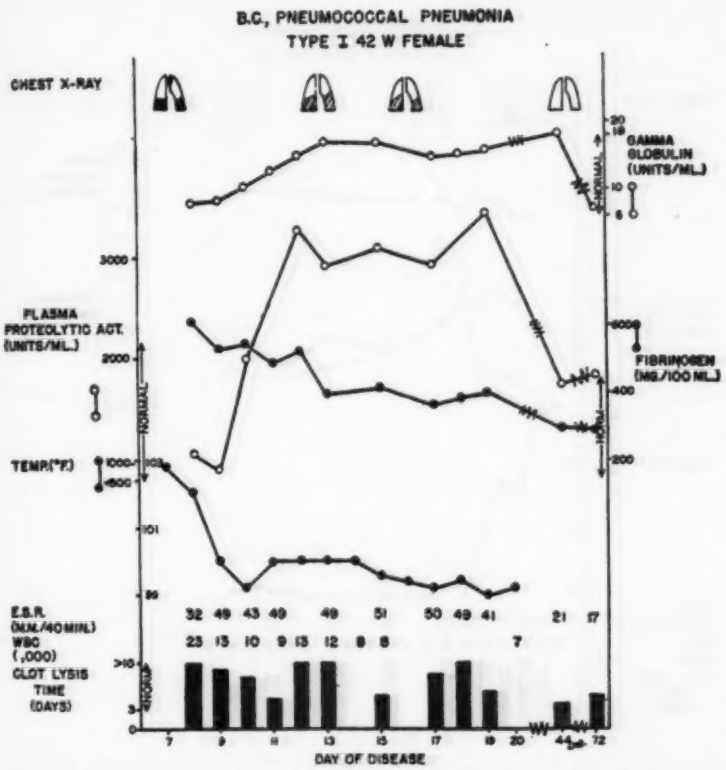

FIG. 3. Changes in clot lysis time, white blood cell count, sedimentation rate, potential plasma proteolytic activity, plasma fibrinogen and plasma gamma globulin in a patient with lobar pneumonia. In this patient, bacterium due to Pneumococcus type I was present on the 8th day of the illness.

highest concentrations of fibrinogen. In the tenth patient, it was greatest the day before the concentration of fibrinogen was at its peak (Figs. 1–6).

This increase in potential proteolytic activity was usually of considerable magnitude. In 6 of the patients, the maximal level of activity was much greater than that found in normal individuals, and in 2

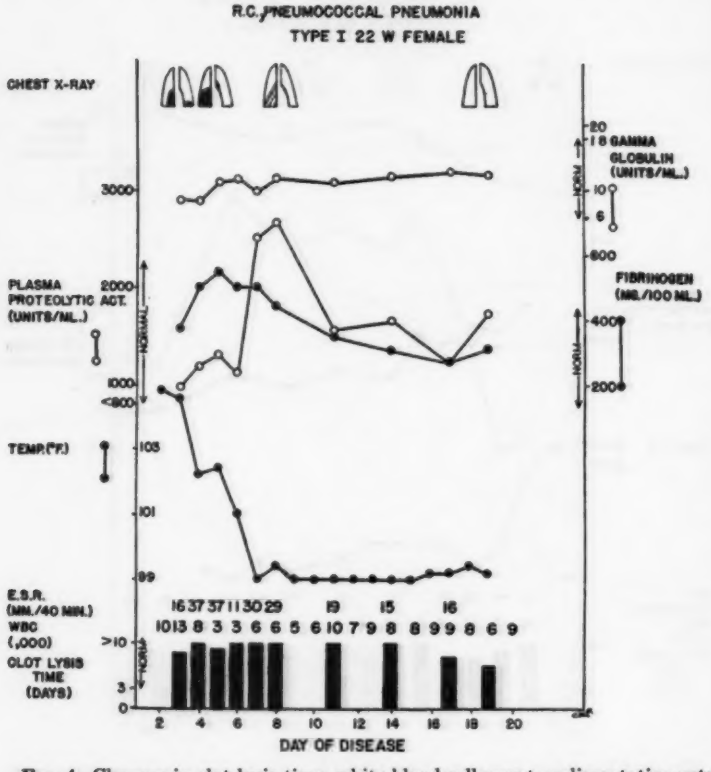

FIG. 4. Changes in clot lysis time, white blood cell count, sedimentation rate, potential plasma proteolytic activity, plasma fibrinogen and plasma gamma globulin in a patient with lobar pneumonia.

of these 6, this potential activity was four or more times greater than that present in the initial sample of plasma. In 3 other patients, the highest titer measured was not greater than that seen in normal individuals, but none the less was increased as much as two

times over the initial level. In the tenth patient, the potential proteolytic activity of plasma rose slowly during the course of her illness, but was always at or near the lowest recordable level (Fig. 6).

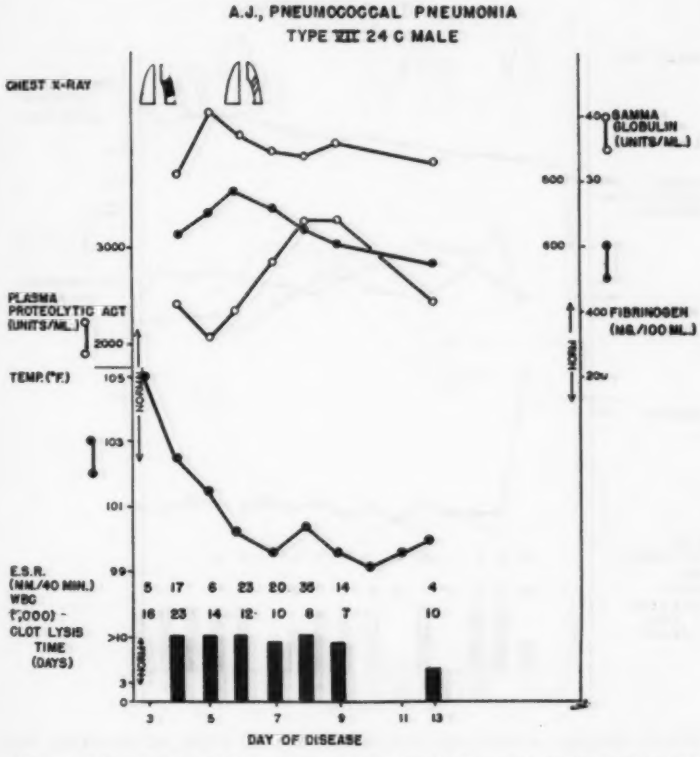

FIG. 5. Changes in clot lysis time, white blood cell count, sedimentation rate, potential plasma proteolytic activity, plasma fibrinogen and plasma gamma globulin in a patient with lobar pneumonia.

In 4 of the patients, it was possible to obtain a sample of blood a month or more after the patient was first studied. In 2 of these patients, the potential proteolytic activity in plasma was appreciably higher late during convalescence than in the initial sample. In the

other 2, the proteolytic activities of the initial and convalescent samples were approximately the same.

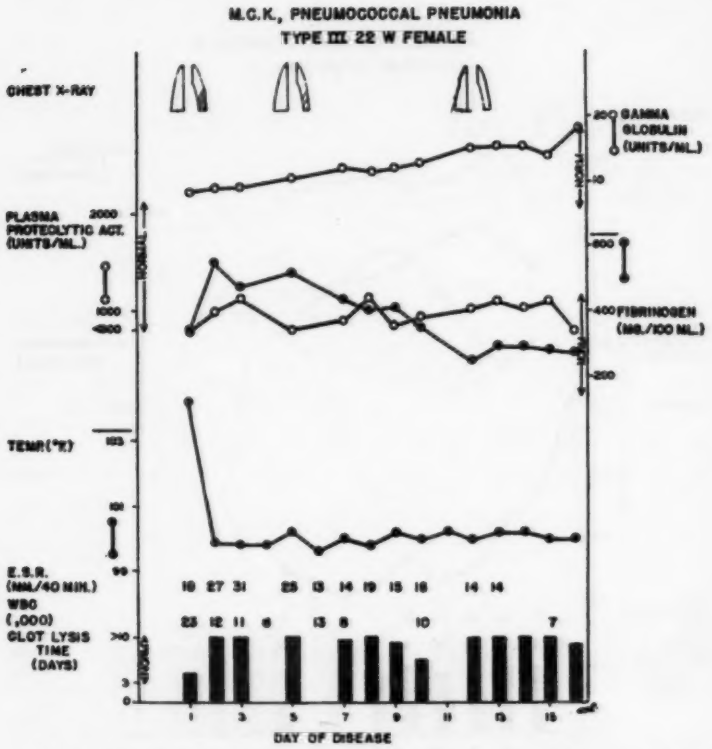

FIG. 6. Changes in clot lysis time, white blood cell count, sedimentation rate, potential plasma proteolytic activity, plasma fibrinogen and plasma gamma globulin in a patient with lobar pneumonia.

4. *Gamma Globulin in Pneumococcal Pneumonia.*—The concentration of gamma globulin in plasma, estimated by Kunkel's indirect method, varied considerably during the course of pneumococcal pneumonia. The data obtained in 6 of the patients are recorded in Figs. 1–6. In each of the patients, the concentration of gamma globulin rose

during the period of observation, although there was considerable variation from day to day. The highest concentration of gamma globulin was present in plasma drawn from the sixth to the nineteenth

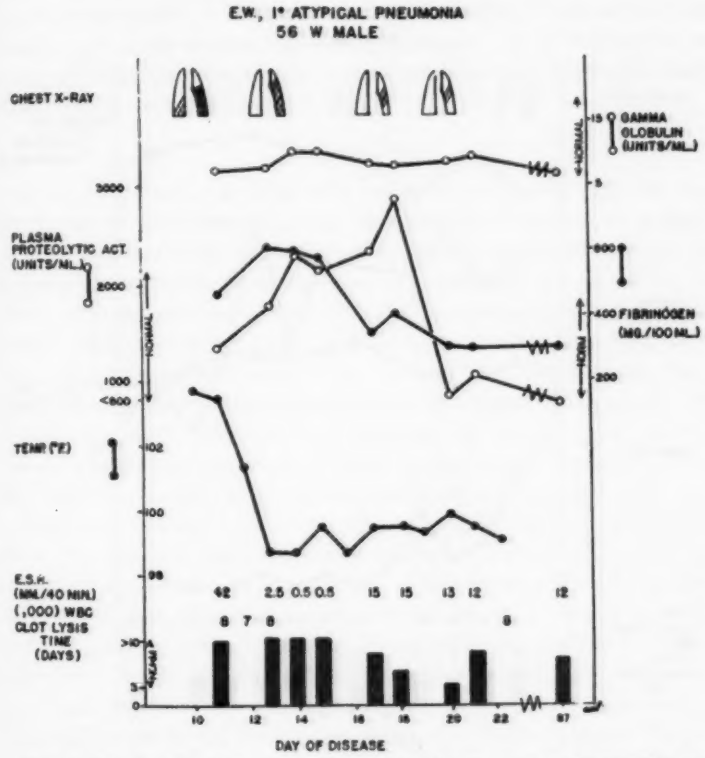

FIG. 7. Changes in clot lysis time, white blood cell count, sedimentation rate, potential plasma proteolytic activity, plasma fibrinogen and plasma gamma globulin in a patient with atypical pneumonia.

day of the patient's illness. No correlation was observed between the concentration of fibrinogen in plasma or the potential proteolytic activity, and the concentration of gamma globulin.

5. *Changes in Fibrinogen, Fibrinolytic Activity, and Gamma Globulin*

in Primary Atypical Pneumonia.—Two patients with primary atypical pneumonia were studied by the techniques which have been described. In 1 of these patients, a 56 year old white male, the same changes

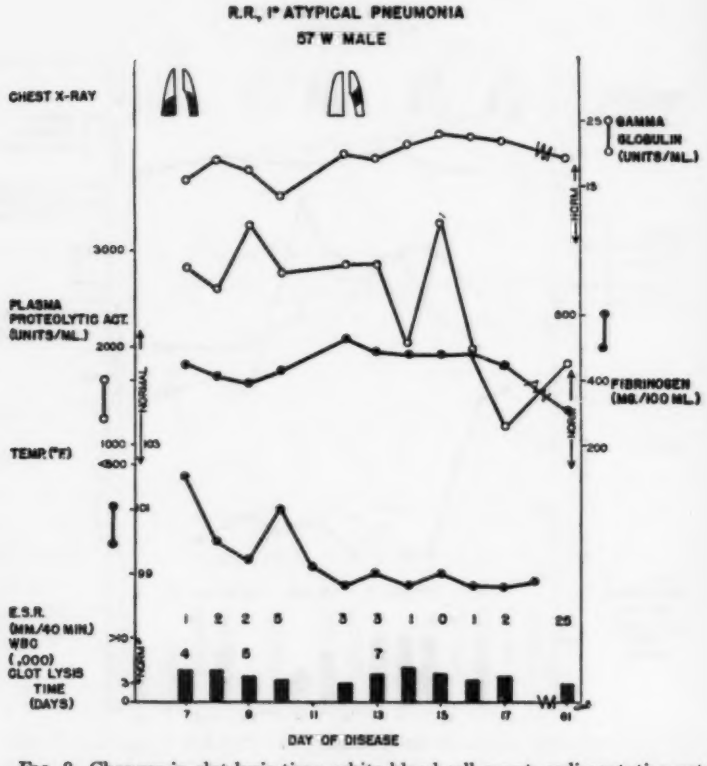

FIG. 8. Changes in clot lysis time, white blood cell count, sedimentation rate, potential plasma proteolytic activity, plasma fibrinogen and plasma gamma globulin in a patient with atypical pneumonia.

were observed that had been noted in the patients with pneumococcal pneumonia. There was a rise in plasma fibrinogen, relative resistance of the plasma clot to spontaneous fibrinolysis, and an increase in potential proteolytic activity in the plasma (Fig. 7). In the second

patient, a 56 year old colored male, the plasma fibrinogen was only slightly elevated during the course of his illness. At the same time, the clot lysis time varied between 3 and 5 days. Late in convalescence, the clot lysis time shortened to 2 days. During the acute phase of the patient's illness, the available proteolytic activity of the plasma was above normal, and during convalescence, it fell. However, no relationship between the concentration of fibrinogen and the available proteolytic activity was apparent (Fig. 8).

DISCUSSION

Gram (1), Foster (2), Ham (3), and others reported that the concentration of fibrinogen in plasma increased above normal in patients with pneumonia, and then decreased during convalescence. In the present investigation, these changes were observed in each of 10 patients with pneumococcal pneumonia. The mechanisms which bring about the increase in fibrinogen concentration have not been elucidated. A number of possible factors may be involved. For example, there may be an increase in the production of fibrinogen, or an increase in the rate of transfer of pre-formed fibrinogen from some labile store to the circulating plasma. Or, perhaps, in patients with acute infections, fibrinogen is removed from the circulation at a diminished rate.

There is in plasma a proteolytic enzyme system capable of digesting fibrinogen (5). Although ordinarily opposed by inhibitory substances present in the plasma (6), the activity of this enzyme system is potentially great. The enzymic activity of just 2 ml. of normal plasma will, under suitable *in vitro* conditions, destroy within 30 minutes fibrinogen equivalent to the amount normally present in the total volume of circulating plasma. The present study indicates that this enzyme system may be one of the factors controlling the concentration of fibrinogen in plasma.

No method is now available to determine the activity of the plasma proteolytic enzyme *in vivo*. Its activity *in vitro* may be estimated by determining the clot lysis time. During the acute phase of pneumonia, when the concentration of fibrinogen in the plasma was increasing, the clot lysis time was longer than late during convalescence. In other words, the fibrinolytic activity of the plasma *in vitro* was relatively low at a time when the concentration of fibrinogen was high. Fibrinoly-

sis is a complex phenomenon, and the clot lysis time may be influenced by many factors. Among these are the concentration of fibrinogen in the plasma, the proteolytic enzyme potentially available in the plasma, and the inhibitory activity of the plasma against plasma proteolytic enzyme. In the present study, no correlation between the clot lysis time and either the amount of fibrinogen or the available proteolytic activity in the plasma was observed. The inhibitory activity of the plasma was not studied. Earlier, it was shown that the inhibitory activity of different plasmas was unstable *in vitro*, and decreased to a variable degree during storage, even in a carbon dioxide refrigerator (16). In the present investigation, only stored plasmas were available for the measurement of inhibitory activity. For this reason, it was not possible to determine inhibitory activity with accuracy.

The spontaneous proteolytic activity of oxalated plasma is only a small fraction of that potentially available. This potentially available proteolytic activity was determined by the addition of purified streptococcal fibrinolysin to diluted plasma. Using this technique, it was demonstrated that in all except one patient with penumococcal pneumonia, the potential proteolytic activity of plasma rose during convalescence and was greatest either simultaneous with or shortly after the fibrinogen concentration was maximal. This change was striking and the activity occasionally reached four times the initial level. The data suggest that this increase in potential proteolytic activity might be a response to the increase in the concentration of fibrinogen, and might account for the subsequent decrease in the fibrinogen concentration. The determination of potential proteolytic activity was made in the presence of any antibodies to the streptococcal fibrinolysin. However, any increase in the titer of these antibodies during the course of the pneumonia would have resulted in a decrease in proteolytic activity by decreasing the effective amount of streptococcal fibrinolysin. On the contrary, the potential proteolytic activity observed was increased.

It is of interest that some years ago Jobling, Petersen, and Eggstein (17) demonstrated that the crisis in patients with untreated pneumococcal pneumonia was associated with an increase in the proteolytic activity of the patient's serum. In their experiments, the serum was first treated with chloroform to decrease the activity of the protease

inhibitors in serum. Jobling and his associates suggested that a causal relationship might exist between the crisis of pneumonia and the changes in serum proteolytic activity.

The changes in the plasma fibrinogen in pneumonia, then, were accompanied by changes in plasma proteolytic activity. When the fibrinogen level was high, during the acute phase of pneumonia, the spontaneous proteolytic activity of plasma was low. This may explain the high levels of fibrinogen noted. Moreover, the available proteolytic activity of plasma rose sharply shortly after the fibrinogen had reached its peak, and may have accounted for its return to normal levels. The complexity of the phenomena under study make it likely that other, alternate interpretations may explain the data reported. However, that a causal ralationship exists between the fibrinolytic properties of plasma and the concentration of fibrinogen in plasma seems an attractive hypothesis.

SUMMARY

(1) In ten cases of pneumococcal pneumonia, the concentration of fibrinogen rose, reaching a peak on the third to tenth day of the patient's illness.

(2) The spontaneous fibrinolytic activity of plasma, measured *in vitro*, was usually relatively low during the acute phase of pneumonia, and increased late during convalescence.

(3) The potential proteolytic activity of plasma, measured after activation with streptococcal fibrinolysin, increased early during convalescence from pneumonia, reaching a peak simultaneous with or just after the concentration of fibrinogen was at its highest level. The maximal potential proteolytic activity was as great as four times the activity present in the first sample of plasma studied.

It is a pleasure to acknowledge the technical assistance of Miss Marjorie Huck and Mrs. Nanita Woodyard.

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RETRACTION OF CLOTS FORMED FROM PURIFIED FIBRINOGEN*

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The fibrin clot is considered to be a network gel. Such gels may undergo spontaneous shrinkage, a phenomenon known as syneresis. Under appropriate conditions the blood clot is capable of exhibiting much more rapid and marked contraction than is seen with simple gels. This phenomenon of clot retraction has received the attention of many investigators but the physical factors involved are not clearly understood. However, it has been well established that clot retraction is poor unless blood platelets are numerous (1, 2).

In preliminary studies in this laboratory, the retraction of whole plasma clots was examined. In these experiments normal human plasma was rendered virtually platelet-free by centrifugation. The plasma samples were allowed to clot in glass tubes and in tubes coated with silicone. Undisturbed clots formed from platelet-free plasma under these conditions invariably failed to show detectable evidence of syneresis within a period of 72 hours at 37°C (3). Acceleration of clotting produced by the addition of thromboplastin, thrombin or finely divided glass did not cause retraction to occur.

In other experiments normal plasma of varying platelet concentration was obtained by mixing platelet-free and platelet-rich plasma in different proportions by a technique previously described (4). In clots formed in these plasmas, the degree of retraction was directly related to the concentration of platelets (3). Retraction was prompt and reproducible in silicone-treated tubes but was delayed and erratic in glass tubes because of adherence of the clot to the glass surface. In silicone-treated tubes retraction was usually complete within one hour at 37°C, the degree of retraction depending upon platelet concentra-

* This investigation was supported in part by a research grant from the Division of Research Grants and Fellowships, National Institutes of Health, U. S. Public Health Service.

tion. When the platelet count was sufficiently low that complete retraction did not occur within one hour, there was little further retraction even after incubation for several days. A small amount of serum was extruded from clots containing as few as 20,000 platelets per mm^3 in silicone-treated tubes. At this platelet concentration retraction was not observed in glass tubes. No evidence of syneresis was detectable in silicone-treated tubes when the platelet count was less than 20,000 per mm^3.

In the present report some factors concerned with retraction of clots formed from purified fibrinogen have been considered. In the experiments to be described retraction of undisturbed fibrin clots did not occur in the absence of intact blood platelets. Even in the presence of platelets there was no retraction unless certain adjuvant substances were present. The rate of retraction was found to be influenced by alterations in the conditions of the physical environment, as well as by variations in the concentrations of the reacting substances.

METHODS

A preparation of dried bovine fibrinogen[1], 95 per cent clottable, was dissolved in barbital buffer to the concentration desired. The buffer solution contained 7.30 gm. sodium chloride, 2.76 gm. barbital and 2.06 gm. sodium barbital in one liter. Phosphate buffer solution of varying pH values were prepared as described by Parker (5). The pH of the buffer solutions was determined with a Beckman Laboratory Model pH meter. Bovine thrombin (Upjohn) was dissolved in 0.85 per cent sodium chloride solution to a concentration of 20 units per ml. Bovine serum albumin (Fraction 5, Armour Laboratories) was dissolved in the barbital buffer.

Syringes, pipettes and test tubes used in the collection and preparation of plasma and platelet suspensions were coated with silicone[2] and with silicone oil.[3] The Pyrex test tubes (internal diameter 11 mm.) in which clot retraction was observed were also treated with silicone

Suspensions of washed platelets were obtained from human blood without the use of anticoagulant. Thirty ml. of blood were drawn from an antecubital vein using silicone-treated equipment. The blood was centrifuged immediately at 3000 rpm in a Sorvall superspeed centrifuge maintained at a temperature of 4°C. After about 5 minutes of centrifugation, 2 ml. of plasma were removed from the upper portion of the tube. Platelet counts on these plasma samples were performed using the Rees-Ecker method (6). Such plasma usually contained from 200,000 to 500,000

[1] Fibrinogen was obtained through the courtesy of Dr. Walter H. Seegers.

[2] Dri-film 9987, General Electric Company.

[3] Silicone oil 9996, 200 centistokes.

platelets per mm.^{3} One ml. of this "platelet-rich" plasma was mixed thoroughly with 9 ml. of barbital buffer in a silicone-treated centrifuge tube. After centrifugation for one minute at 1000 rpm in an International centrifuge the upper 9 ml. of fluid were discarded. The remaining one ml. of platelet suspension was agitated gently and platelet counts were again performed. Values of 80,000 to 150,000 platelets per mm.^{3} were usually obtained.

"Platelet-free" plasma was prepared by centrifuging human blood at 12,000 to 14,000 rpm in the refrigerated Sorvall centrifuge for 10 minutes. In some instances no anticoagulant was used. In most experiments the blood was oxalated by the addition of one part of 0.1 M sodium oxalate to 9 parts of blood.

The serum used in these experiments was prepared from human platelet-free plasma. One part of thrombin solution (20 u/ml.) was mixed with 10 parts of plasma. Ten minutes after coagulation occurred, the clot was compressed. After incubation for 30 minutes at 37°C., the serum was removed.

Protein fractions of normal human serum were prepared in the following manner. Forty ml. of platelet-free serum were mixed with 40 ml. of distilled water and 40 ml. of neutral saturated ammonium sulfate solution. The precipitate was washed in one-third saturated ammonium sulfate, resuspended in 8 ml. of 0.85 per cent sodium chloride solution, and dialyzed in a cellophane bag against barbital buffer (pH 7.5) for 14 hours at 2°C.

The entire supernate of the first precipitation was mixed with 40 ml. of saturated ammonium sulfate. The precipitate was washed in half-saturated ammonium sulfate and dialyzed as previously described. The fluid remaining after precipitation was also dialyzed against the buffer. The albumin and globulin fractions obtained in this way were tested for their ability to enhance clot retraction.

For the observation of clot retraction, fibrinogen solution and other test substances were mixed in silicone-treated test tubes to which thrombin solution was finally added. The tubes were quickly shaken before clotting took place and were then allowed to stand undisturbed in a water bath at 37°C. Retraction, when it occurred, was prompt, and there appeared to be little tendency for the clot to adhere to the silicone surface.

EXPERIMENTS

1. *Conditions required for the retraction of clots formed from purified fibrinogen.* A solution of purified bovine fibrinogen was clotted in silicone tubes by the addition of bovine thrombin. The clots which formed under these conditions showed no visible evidence of syneresis. The addition of a suspension of washed human platelets to the fibrinogen solution did not cause the clots to retract. However, when a small amount of human serum in addition to platelets was present in the fibrinogen solution, prompt clot retraction occurred. When other factors were constant, the degree of retraction of the clots was related to

the concentration of serum added. The results of a typical experiment are shown in Table I and in Fig. 1. This experiment demonstrated

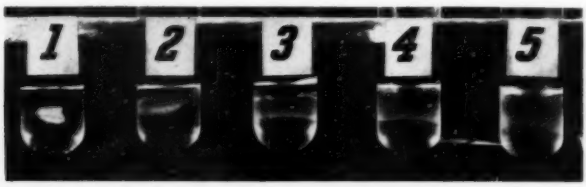

FIG. 1. The relationship between serum concentration and degree of clot retraction. The data of this experiment are given in Table I. Tube 6, not included in the photograph, contained no serum and showed no retraction. In the other tubes, the degree of retraction was related to the amount of serum added. The photograph was made 24 hours after clotting.

TABLE I

Relationship between serum concentration and clot retraction

TIME AFTER CLOTTING	FINAL CONCENTRATION OF SERUM					
	10%	8%	6%	4%	2%	0
	Tube 1	2	3	4	5	6
	Degree of Clot Retraction					
hours						
1	++++ ++++	+++ +++	+++ +++	++ ++	++ +	0 0
4	++++ ++++	+++ +++	+++ +++	++ ++	++ ++	0 0
24	++++ ++++	+++ +++	+++ +++	++ ++	++ ++	0 0
	Time after Clotting of Appearance of Detectable Retraction (min.)					
	9, 7	7, 11	9, 10	30, 30	17, 20	

0.1 ml. of 1% fibrinogen solution was mixed with 0.5 ml. of platelet suspension (platelet count 102,000 per mm³) and 0.4 ml. of various dilutions of human serum. This mixture was clotted by the addition of 0.1 ml. thrombin solution (20/uml.). Clotting occurred in all tubes in 40–45 sec. after addition of thrombin. The tubes were incubated at 37°C and observed for clot retraction for 24 hours. The time at which retraction was first detected is recorded. All of the determinations were in duplicate. The tube numbers correspond to those in Figure 1.

that fibrin clots do not retract, even in the presence of platelets, unless additional serum components are present.

An attempt was made to identify the serum factor required for the

occurrence of retraction. Normal human serum was fractionated with various concentrations of ammonium sulfate. Each fraction obtained was examined for its effectiveness in promoting clot retraction. The results of this study indicated that each of the serum fractions tested was active at a concentration less than that in serum.

Bovine serum albumin was found to be an entirely satisfactory replacement for human serum in enhancing clot retraction. Retraction occurred in the presence of bovine albumin in concentrations as low as 0.1 mg. per ml. A number of other substances not derived from blood were also found to be effective. These included gum acacia in a con-

TABLE II

Relationship between platelet concentration and clot retraction

	FINAL CONCENTRATION OF PLATELETS (THOUSANDS PER MM^3)											
TIME AFTER CLOTTING	0		26		52		78		104		130	
	Tube 1		2		3		4		5		6	
	Degree of Clot Retraction											
hours												
1	0	0	0	+	+	++	++	++	++	++	++	++
24	0	0	0	+	+	+++	+++	+++	++++	++++	++++	++++

0.1 ml. of 1% fibrinogen solution was mixed with 0.1 ml. of human serum and with 0.8 ml. of platelet suspension of varying concentration. This mixture was clotted by the addition of 0.1 ml. of thrombin solution (20 u/ml.). Clotting occured in all tubes in 10–20 sec. after addition of thrombin. The tubes were incubated at 37°C and observed for clot retraction for 24 hours. Duplicate determinations were made. The tube numbers correspond to those in Figure 2.

centration of 6 mg. or more per ml. and egg white. On the other hand tyrosine (0.1 to 1.0 mg. per ml.) and glycine (0.5 mg. per ml. to 8.0 mg. per ml.) were without effect. Sodium desoxycholate in concentrations ranging from 0.07 to 0.60 mg. per ml. was also ineffective.

2. *Platelets and clot retraction.* In the presence of serum or an effective substitute, the degree of retraction of clots formed from purified fibrinogen was related to the concentration of platelets in the preparation (Table II). Retraction occurred promptly and was often complete within one hour. Prolonged incubation at 37°C did not appreciably increase the degree of retraction. Retraction did not occur in the

presence of serum when platelets were absent. Intact platelets were required, and suspensions of macerated platelets were without effect in promoting clot retraction. When a platelet suspension was frozen and thawed, there was complete loss of ability to produce retraction Similarly, platelets heated to 45°C for 10 minutes were inert. In some

FIG. 2. The relationship between platelet concentration and degree of clot retraction. The data of this experiment are given in Table II. The degree of retraction was related to platelet concentration, which ranged from 0 to 130,000 per mm^3.

TABLE III

Relationship between fibrinogen concentration and clot retraction

TIME AFTER CLOTTING	FINAL CONCENTRATION OF FIBRINOGEN (PER CENT)			
	0.1	0.2	0.3	0.5
	Tube 1	2	3	4
	Degree of Clot Retraction			
hours				
5	++++ ++++	+++ +++	++ ++	+ +
20	++++ ++++	+++ ++++	++ ++	+ +

0.4 ml. of platelet suspension (70,000 per mm^3) were mixed with 0.1 ml. of human serum and 0.5 ml. of fibrinogen solution of varying concentration. This mixture was clotted by the addition of 0.1 ml. of thrombin (20 u/ml.). Clotting occurred in 20–25 sec. The tubes were incubated at 37°C. Duplicate determinations were made. The tube numbers correspond to those in Figure 3.

experiments powdered charcoal and glass dust were substituted for platelets. These foreign particles did not bring about clot retraction.

3. *Fibrinogen and clot retraction.* When the concentration of platelets, thrombin and serum were maintained at constant values, the degree of clot retraction was inversely related to the concentration of fibrinogen. Retraction was more pronounced in clots formed from dilute fibrinogen solutions (Table III). More platelets were required to

cause retraction of clots formed from relatively concentrated fibrinogen solutions than were required when the concentration of fibrinogen was low.

4. *Thrombin and clot retraction.* When fibrinogen, platelets and serum were present in adequate amounts, the degree of clot retraction varied

FIG. 3. The relationship between fibrinogen concentration and degree of clot retraction. The data of this experiment are given in Table III. The degree of retraction was inversely related to fibrinogen concentration, which ranged from 0.1 to 0.5 per cent.

TABLE IV

Relationship between thrombin concentration and clot retraction

HOURS AFTER CLOTTING	FINAL CONCENTRATION OF THROMBIN (UNITS PER ML.)					
	1.0		0.5		0.1	
	Clotting time in seconds					
	30	35	80	85	150	150
	Degree of clot retraction					
1	+++	+++	+	+	+	+
24	+++	+++	+	+	+	+

0.1 ml. of 1% fibrinogen solution was mixed with 0.5 ml. of platelet suspension (platelet count 54,000 per mm^3) and 0.1 ml. of human serum. The mixture was clotted by the addition of 0.1 ml. of thrombin solutions of varying strengths. The tubes were incubated at 37°C and observed for clot retraction for 24 hours. All determinations were done in duplicate.

with the concentration of the thrombin solution employed (Table IV). Since the preparation of thrombin used was not chemically pure, it is not known that this effect is attributable specifically to thrombin.

5. *pH and clot retraction.* Washed human platelets were suspended in a series of phosphate buffers ranging in pH from 5.92 to 8.15. Phenol red was added to each preparation after which fibrinogen, human

serum and thrombin were introduced. The absence of a detectable color change indicated that there was no appreciable change in the pH during the mixing process. The results of this experiment are recorded in Table V. It is apparent that retraction was not measurably influenced by pH changes within the range studied.

6. *Temperature and clot retraction.* Clots formed from purified fibrinogen in the presence of platelets and human serum were observed for retraction at different temperature levels. Retraction occurred within 30 minutes at 37°C and was usually complete within 1 hour. Retraction did not occur when the clot was maintained at 2°C, although it took place promptly when the specimen was warmed to 37°C. Clots

TABLE V

Relationship between pH and clot retraction

HOURS AFTER CLOTTING	pH 5.92	pH 6.5	pH 7.3	pH 8.15
	Degree of retraction			
1	++ ++	++ ++	++ ++	++ ++
24	++++ ++++	++++ ++++	++++ ++++	++++ ++++

Solutions of varying pH were obtained using Sørenson phosphate buffers.

0.1 ml. of 1% fibrinogen solution was mixed with 0.5 ml. of platelet suspensions in buffers of varying pH and 0.1 ml. of bovine albumin (30 mg. per ml.). A drop of phenol red indicator was added to each tube. The mixture was clotted by the addition of 0.1 ml. of thrombin solution (20 u/ml.). Clotting occurred in all tubes in 20–25 sec. after the addition of thrombin. The tubes were incubated at 37°C and observed for clot retraction. All of the determinations were in duplicate. No change in pH occurred after clotting as shown by phenol red.

kept at 2°C for as long as 36 hours retracted at the end of that time when the temperature was raised to 37°C. Retraction appeared to be as prompt and complete at 27°C as at 37°C. When clots were incubated at 45°C for only 10 minutes, retraction did not occur and the ability to retract was permanently destroyed.

7. *Salt concentration and clot retraction.* The effect of salt concentration on clot retraction was studied in a system in which sodium chloride was essentially the only electrolyte present. In these experiments fibrinogen and thrombin solution and platelet suspensions were prepared using sodium chloride solutions of varying concentrations. When the electrolyte concentration was reduced to about one-half that of

normal serum, retraction occurred normally. However, when the concentration of salt was more than twice that of normal serum, retraction was entirely inhibited.

DISCUSSION

The retraction of whole plasma clots has been studied by Fonio (7), Tocantins (8), Lampert and Ott (9), Opitz and Schober (10), and in particular detail by Werner (11, 12, 13). It is generally agreed that plasma clots formed in test tubes in the absence of platelets exhibit no retraction if left undisturbed.

Denys (14), Hayem (1), and Opitz and Schober (10) observed that clot retraction was poor or lacking in thrombocytopenic blood. In recent experiments it has been possible to demonstrate a direct relationship between platelet concentration and clot retraction in plasma in which other factors are kept constant (3, 15). The manner in which platelets exert this effect is unknown. A number of previous investigators (2, 12) have demonstrated that intact platelets are necessary and that platelet extracts are ineffective.

In the present study the retraction of clots formed from purified fibrinogen was observed. Clots formed from purified bovine fibrinogen failed to retract even in the presence of intact platelets. When a small amount of serum was present in addition to platelets, retraction did occur. When fibrinogen, platelet and thrombin concentrations were constant, retraction was proportional to the concentration of serum. This appeared not to be a specific effect of serum, since gum acacia, bovine albumin, and human albumin and globulin fractions exhibited the same property. Laki (16), also, has observed that clots formed from purified fibrinogen do not retract unless serum is present. The mechanism by which the adjuvant substance exerts its effect is unknown. However, the effect may be dependent upon the presence of molecules of colloidal size. Simpler substances tested were without effect. Fibrin clots did not retract in the presence of serum unless platelets were also present.

When purified fibrinogen was clotted by thrombin in the presence of platelets and serum, the degree of retraction was influenced by the concentration of each of these four components. When the other factors were constant, the degree of retraction was directly related to the

concentration of platelets. On the other hand, when the platelet concentration was constant, the degree of retraction was inversely proportional to fibrinogen concentration. Dense fibrin clots required higher concentrations of platelets for retraction than clots formed from more dilute fibrinogen solutions. Clot retraction was somewhat impaired at lowered concentrations of thrombin. A relationship between thrombin and retraction has also been noted by Jürgens and Studer (17) and by Quick (18).

The rate and degree of retraction were influenced by temperature and ionic concentration, but pH alterations between pH 6.0 and pH 8.3 were without effect. Retraction was inhibited at low temperatures. However, clots maintained at low temperature for a long time retracted promptly upon return to body temperature, provided that freezing had not occurred. After freezing, platelets were no longer capable of inducing clot retraction, an observation previously made by Werner (12). Similarly, heating platelets to only 45° for ten minutes permanently destroyed their ability to produce retraction. Clot retraction was inhibited by an increase of salt concentration to approximately double that of normal plasma; however, reduction of salt concentration to approximately half that of normal plasma was without detectable effect.

SUMMARY

The retraction of clots formed from purified fibrinogen was studied. Fibrin clots did not retract in the absence of blood platelets. Even in the presence of platelets, retraction did not occur unless serum or certain other colloidal substances were also present. The degree of retraction was directly related to the concentration of platelets, of serum, and of thrombin, and inversely related to the concentration of fibrinogen. The effects of changes in temperature, salt concentration and pH were observed.

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THE EFFECTS OF ACTH AND CORTISONE ON ANTIBODIES IN HUMAN BEINGS

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The relation of the adrenal glands to protein metabolism, and in particular to the formation and release of antibody, has been the subject of considerable investigation and controversy. Changes in the serum proteins, the level of pre-existing antibody and the rate of antibody formation under conditions of adrenal suppression and stimulation have been studied by many workers in a variety of animal species. Some of the results seem to be conflicting and will be considered in the discussion.

The observations concerning human beings, however, have shown consistency and agreement. McCullagh and Lewis (1) studied the electrophoretic patterns of the plasma proteins in 19 patients with Addison's disease. When there were signs of adrenal insufficiency, the total protein was at the upper range of normal with a decrease in the percentage of albumin and some increase in all globulin fractions. Replacement therapy with adrenal cortical extract (ACE) resulted in a return to normal values. No change was noted in the plasma protein patterns of a few normal human beings treated with adrenocorticotropic hormone (ACTH) (2, 3) but Forsham et al. (3) reported a rise in albumin and a reciprocal fall in alpha 2 globulin but not in gamma globulin in a patient with pituitary insufficiency treated with this hormone. Others also (4, 5, 6) have noted a rise in albumin and/or a fall in gamma globulin in chronically ill patients after several days treatment with ACTH, and similar observations have been made in chronically ill patients treated with cortisone (7).

These studies were carried out in part under contract with the Office of Naval Research and in part with support of a grant-in-aid from the United States Public Health Service.

Since antibody is generally conceded to constitute at least part of the globulin fraction of plasma, and since ACTH and cortisone have proven to be effective in treating patients with diseases due to hypersensitivity, it seemed of interest to study the level of pre-existing antibody, and antibody synthesis, in patients treated with ACTH or cortisone. Herbert and de Vries (8) found no change, within 48 hours after ACTH injection, in the antibody titer of 3 immunized human beings, but McEwen et al. (4) described a decrease in the titer of antistreptolysin in 2 of 3 patients with rheumatic fever after several days treatment with ACTH. We have reported previously in abstract (9) that the treatment of human beings with ACTH or cortisone did not suppress antibody synthesis. A more complete presentation of these studies is the subject of the present report.

EXPERIMENTAL

A total of 59 patients were vaccinated with a mixture of pneumococcal polysaccharides. Seventeen of these patients were subsequently treated with ACTH, 12 others with cortisone, and 30 were untreated. In each case the antibody titer to pneumococcus type II was measured before vaccination or treatment and at intervals up to 21 days after vaccination.

It was decided to test the antibody to pneumococcus type II because Heidelberger et al. (10) observed that the antibody response in human beings to this type polysaccharide was somewhat more regular than that to the other types they studied.

In addition the effect of treatment on pre-existing antibodies, agglutinins to typhoid bacilli and/or isohemagglutinins, was tested in 11 patients. The globulin content of all sera was measured by the Zn sulfate turbidity method of Kunkel (11, 12). Skin sensitivity to pneumococcal polysaccharide (13) was tested in 11 treated and 9 untreated patients. The results of these studies are reported below.

MATERIALS AND METHODS

Patients.—Certain essential data concerning all the patients are recorded in Table I. The 29 patients who received ACTH* or cortisone were admitted to the

* Part of the ACTH used in this study was Actarmour, furnished through the courtesy of Dr. John R. Mote.

Johns Hopkins Hospital for treatment of some chronic disease. Thirteen had asthma and/or allergic rhenitis; 9 others had some form of collagen disease (lupus erythematosis, lupus dissemenata, skin lupus or periarteritis nodosa); 6 others had rheumatoid arthritis, and one had macular degeneration of unknown etiology. Most of these patients have been reported in detail elsewhere (14). The 30 controls included 7 healthy young adults and 23 patients, mostly with chronic disease, selected at random on the medical or surgical wards, with the following diagnoses: coronary disease, 4; inactive rheumatic heart disease, 4; fracture, 4; tuberculosis, 3; carcinoma, 2; nephritis, 1; chronic colitis, 1; bronchiectasis, 1; hypertension, 1; coarctation of the aorta, 1; malnutrition, 1. All of the patients were white. The treated group comprised 13 males and 16 females with an average age of 46 years; the control group, 21 males and 9 females with an average age of 34 years.

Vaccination.—Each patient was vaccinated subcutaneously with a single injection of 1 ml. of a solution containing 0.06 mg. each of the capsular polysaccharides of pneumococcus types I, II, III, V, VII, and VIII (Squibb combination A).†

Sera.—Sterile blood was obtained from each of the patients before vaccination except in the case of 3 patients who were treated with cortisone; from 2 the first blood sample was obtained on the day after vacciation and from one, 3 days after vaccination. All the initial blood samples were procured before treatment was started except 4 which were obtained on treatment day 2, 3, 3, and 5, respectively. The clotted blood was allowed to stand overnight. Then the serum was removed and stored in stoppered tubes under sterile conditions at 4°C. until tested.

Determination of Antibody to Pneumococcus.—Mouse protective antibody against pneumococcus type II, one of the 6 types included in the vaccine, was measured by a neutralization technique similar to that described by Finland and Brown (15). All sera were inactivated by heating at 56°C. for 30 minutes before testing. Each of a series of 10 gm. swiss mice was injected intraperitoneally with 0.1 cc. of a 1:2 dilution of the serum to be tested. Eight serial ten-fold dilutions of an 18-hour blood broth cultures of a strain of pneumococcus type II of known virulence (16) were made in trypticase soy broth (BBL). Then 0.5 cc. of each dilution was injected immediately into normal mice and mice which had previously received the serum injection. This strain of pneumococcus regularly killed normal mice at a dilution of 10^{-7} and occasionally at 10^{-8}. All the animals were observed for 4 days and deaths recorded. One to three mice were employed for each dilution of pneumococcus and most of the sera were tested at least twice by this method. The neutralizing capacity of the serum is expressed as the logarithm of the number of minimal lethal doses (MLD) survived.

Determination of Agglutinins for Typhoid Bacilli and Iso-agglutinins for Erythrocytes.—Agglutinins for the "H" antigen of typhoid bacilli were determined in 15 treated patients. Starting with a serum dilution of 1:5, serial two-fold dilutions

† The pneumococcal polysaccharide was kindly furnished by E. R. Squibb and Sons, New York, through the courtesty of Dr. L. B. Hobson.

TABLE I

Essential Data Concerning Patients

SERIES NO.	J.H.H. NO.	AGE	SEX	TREATMENT	DIAGNOSIS
1	528084	57	M	ACTH	Periarteritis nodosa
2	515486	42	M	ACTH	Rheumatoid arthritis
3	111797	40	M	ACTH	Allergic rhinitis
4	501965	46	M	ACTH	Macular degeneration
5	497902	54	F	ACTH	Rheumatoid arthritis
6	170223	47	F	ACTH	Asthma
7	485051	21	F	ACTH	Lupus erythematosis
8	521267	63	F	ACTH	Collagen Disease
9	527865	46	F	ACTH	Asthma
10	435221	27	F	ACTH	Allergic rhinitis; asthma
11	536620	30	F	ACTH	Disseminated lupus
12	230194	63	M	Cortisone	Asthma
13	523671	51	M	Cortisone	Asthma
14	526560	30	F	Cortisone	Skin lupus
15	434666	53	F	Cortisone	Asthma
16	521688	47	F	Cortisone	Disseminated lupus erythematosis
17	231975	65	F	Cortisone	Rheumatoid arthritis
18	532488	37	F	Cortisone	Lupus erythematosis
19	530174	40	M	Cortisone	Allergic rhinitis; asthma
20	495127	36	F	Cortisone	Disseminated lupus erythematosis
21	512303	34	M	Cortisone	Allergic rhinitis; asthma
22	540714	53	M	Cortisone	Rheumatoid arthritis
23	521968	29	M	Neither	Neprhritis
24	462876	57	M	Neither	Coronary thrombosis; Diabetes
25	488949	45	M	Neither	Chronic colitis
26	523360	74	M	Neither	Carcinoma
27	486435	27	F	Neither	Tuberculosis
28	349030	26	F	Neither	Tuberculosis; pregnancy
29	520815	24	F	Neither	Tuberculosis; diabetes
30	498563	32	F	Neither	Rheumatic heart disease
31	519365	58	M	Neither	Carcinoma
32	522895	53	M	Neither	Coronary thrombosis
33	517502	45	M	Neither	Coronary thrombosis
34	457392	37	M	Neither	Bronchiectasis
35	519568	38	M	Neither	Rheumatic heart disease
36	526385	32	M	Neither	Coarctation of the aorta
37	GSM	40	M	Neither	No Disease
38	ODR	33	M	Neither	No Disease
39	MH	29	F	Neither	No Disease
40	JM	29	M	Neither	No Disease
41	NW	23	F	Neither	No Disease
42	494325	16	M	Neither	Rheumatic heart disease

TABLE I—*Continued*

SERIES NO.	J.H.H. NO.	AGE	SEX	TREATMENT	DIAGNOSIS
43	551547	47	F	Neither	Hypertension
44	549620	19	M	Neither	Fracture
45	550492	38	M	Neither	Fracture
46		34	M	Neither	Fracture
47	336367	42	M	ACTH	Asthma
48	471043	47	F	ACTH	Rheumatoid arthritis
49	231977	66	M	ACTH	Asthma
50	464514	37	M	ACTH	Lupus erythematosis
51	528824	57	M	ACTH	Asthma
52	118083	56	F	ACTH	Asthma
53	210159	47	F	Cortisone	Rheumatoid arthritis
54	523825	49	M	Neither	Coronary thrombosis
55	501677	50	F	Neither	Rheumatic heart disease
56	492212	32	F	Neither	Malnutrition
57	550833	69	M	Neither	Fracture
58	JMS	32	F	Neither	No Disease
59	IMS	28	M	Neither	No Disease

were made in physiological saline and an equal volume of antigen (turbidity McFarland #3) was added. The mixtures were kept at 37°C. for 2 hours, then in the refrigerator at 4°C. overnight, and gross clumping estimated. The blood group of 18 treated patients was determined by standard methods. Then two per cent suspensions in physiological saline of thrice washed erythrocytes type A and B were prepared. Type A cells were added to types B and O sera; type B cells to type A sera. The appropriate cell suspension was added in equal volume to serial two-fold dilutions, in physiological saline, of the serum to be tested. These mixtures were kept at 37°C. for 2 hours and then at 4°C. overnight. They were then warmed to room temperature and examined for gross clumping. All the sera from each patient were tested.

Measurement of Globulin.—The globulin content of all sera was measured by the Zn Sulfate turbidity method described by Kunkel (11, 12). The reagent was prepared by dissolving 24 mg. of $ZNSO_4 \cdot 7H_2O$, 280 mg. of barbital and 210 mg. of sodium barbital in 1000 ml. of distilled water. One volume (0.05 ml.) of serum was added to 60 volumes (3 ml.) of the reagent. The mixture was allowed to stand for 30 minutes at room temperature, shaken, and the turbidity measured in a Coleman Junior Spectrophotometer at a wave-length of 650 mμ. The units were determined by reference to a standard curve.

Skin Sensitivity.—The dermal sensitivity (13) of 20 patients to pneumococcal polysaccharide was determined by injecting intradermally into the skin of one forearm 0.1 cc. of the polysaccharide mixture used for vaccination. Into the other forearm 0.1 cc. of physiological saline was injected. The sites of inoculation were

observed 30 minutes after injection. The site of saline injection showed no reactions in any case. The diameter of any wheal and/or erythema about the site of polysaccharide injection was measured in each case.

RESULTS

The mouse protective titers against pneumococcus type II was determined on each serum sample by the method previously described. It was found that the sera obtained before vaccination from 13 patients of the 59 patients tested, or 22%, had mouse protective titers against 100 or more MLD's of pneumococcus type II. MacLeod et al (17), in a similar study found mouse protective antibody against pneumococcus type II in 2 of 8 patients tested before vaccination, and Heidelberger et al. (10), using a quantitative precipitin technique, detected some antibody against pneumococcus type II polysaccharide in 11 of 29 patients tested before vaccination. These workers observed considerable variation in the antibody response of 20 patients to a single injection of vaccine similar to the one used in the present study. One failed to develop any antibody; 5 had a slightly higher titer at 2 weeks than at 6 weeks; and in the remaining 14 a somewhat higher titer was found at 6 weeks.

Since it is generally believed that previous immunity enhances the speed and degree of antibody production by an animal upon subsequent exposure to the antigen, it was decided to eliminate from our comparative analysis all patients whose pre-vaccination sera neutralized more than 10 MLD's of the pneumococci. The results in the remaining 46 patients are summarized in Tables II and III. Twenty-two of the patients (Table II) received either ACTH or cortisone during the post-vaccination period and 24 control patients (Table III) did not receive either of these drugs. For purposes of analysis, the data are grouped into 4 time intervals: before vaccination, 1–4 days, 5–10 days, and 11–21 days after vaccination. It will be seen that the geometric mean titer of neutralizing antibody before vaccination was slightly greater (0.58 log) in the control group than in the treated group of patients (0.41 log). In the next two intervals chosen, however, the mean titer in the treated group was somewhat greater than in the controls. This is true despite the fact that the average time following vaccination was a little greater in the control group. The difference in mean titer is greater in the 10–21 day interval, where 5.41 logs was found in the

TABLE II

Mouse Protective Antibodies In Patients Treated with ACTH or Cortisone

PATIENT NO.	TREATMENT		DAY AFTER VACCINATION																				
	Drug	Dose, mg.†	−2	−1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
1	ACTH	1935			1*		1											5				7				
2	ACTH	156			1						1															
3	ACTH	425			1							7		7					7							
4	ACTH	720			1								7							7						
5	ACTH	557			1							3														6
6	ACTH	470			0		2					4								3						
7	ACTH	580			0							5										6				
8	ACTH	690			0							1										2				
9	ACTH	570			1									5					7							
10	ACTH	725			0					2						2									3	
11	ACTH	468			0			0			1															
12	Cort.	1300				1						3	4							6						7
13	Cort.	900			0						0		5							6						
14	Cort.	1185			0				0	3		6														
15	Cort.	900			1			1		1		2							6							
16	Cort.	1200			0						0							5								
17	Cort.	1105				1		1		3		6						6								
18	Cort.	2121			0					2							4		5							
19	Cort.	2300			0								5													5
20	Cort.	895			0																	4				
21	Cort.	1250						0				4														
22	Cort.	800			0			0					4													
Average Titer‡					0.41			0.88				3.70							5.41							
Average Day§								3.1				7.0							15.6							

* Each digit represents the log of the number of MLD's neutralized by 0.05 ml. of serum.

† The amount of drug administered between the times of vaccination and the last serum tested. The bar represents the duration of treatment.

‡ Average of the highest titers observed in each time interval.

§ Average of the last day tested in each time interval.

treated series, as compared with 3.75 logs in the controls. The average time after vaccination was 15.6 days in the treated series and 14.9 days in the controls. The observed difference in titer (1.66 logs), when

TABLE III

Mouse Protective Antibodies in Control Patients

PATIENT NO.	DAY AFTER VACCINATION																				
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
23	1*							0				3			3			0				
24	1							1				0			0			0				
25	1							6				3			1			1				
26	1							0				0			1							
27	1							5				6			6			6				
28	1							0				2			0			0				
29	0							3				3			4			3				
30	1							6				5			3			3				
31	0				2		2	7				6										
32	1				0		1	1				6										
33	1				0		0	0				1										
34	1				0		0	3				3										
35	1				0		1	3				3										
36	0				0		0	5														
37	0			3						6								4				
38	0			0						4												
39	0			0						4								4				
40	1			1						3								3				
41	1			1						3								7				
42	1			0					4													
43	0			0				4							4							
44	0			0					4						4							
45	0				0				3						5							
46	0			0				3							5							
Average Titer†	0.58			0.44				3.25										3.75				
Average Day‡				3.4				8.1										14.9				

* Each digit represents the log of the number of MLD's neutralized by 0.05 ml. of serum.

† Average of the highest titers observed in each time interval.

‡ Average of the last day tested in each time interval.

divided by the standard error of the difference (0.53 logs), gives a value of 3.1. The probability of getting a difference this great or greater just by chance is less than 1/500. Since too few mice were

used to obtain statistically accurate endpoints to all the titrations, it can be concluded only that the treatment of human beings in the present series with ACTH or cortisone did not suppress antibody formation and probably had some enhancing effect.

Effects of ACTH or Cortisone Treatment on Anti-typhoid Agglutinins and Isohemagglutinins.—The agglutinins for typhoid H antigen were measured, by the method described above, in 15 patients who received treatment with ACTH or cortisone. Five were found to have agglutinins in a titer of 1:10 or greater. Serial determinations were carried out with the serum from these patients throughout the period of their treatment. The blood type of 15 treated patients was determined and 11 were found to be type A, B, or O. Isohemagglutinins for erythrocytes of a different blood type were determined serially in these 11 patients, 7 treated with ACTH and 4 with cortisone. The results of these agglutination tests are summarized in Table IV. It will be seen that in two patients (No. 4 and 5), the titer of typhoid agglutinins became 4 to 8-fold lower during treatment while in the 3 other patients tested, no obvious change in titer occurred. The titer of isohemagglutinins in 5 (No. 5, 6, 7, 12, and 13) of the 11 patients tested was 4-fold higher during treatment than before.

Studies of Serum Globulin.—All sera were tested by Kunkel's technique (11, 12) for their content of globulin. The values obtained for the first and last serum from each patient tested are presented in Tables V, VI, and VII. It will be seen that the serum globulin measured by this method decreased in a majority (13/17) of the patients during treatment with ACTH, an average fall in the whole group of 3.2 units. In the 12 cortisone treated patients 6 showed a fall in globulin; 2, no change; and 4, a rise with an average gain of 4.4 units for the whole group. In the control sick group an increase or decrease in globulin was noted with about equal frequency. No changes were noted in the 5 normal controls.

It is of interest that there is no obvious correlation in any group between the development of anti-pneumococcal antibodies and changes in the serum globulin, measured by the Zn Sulfate method. Moreover, a considerable fall in the total globulin measured by this technique is not incompatible with a rising titer of specific antibodies.

The Effect of ACTH and Cortisone on Dermal Sensitivity.—The

TABLE IV

Agglutination of Typhoid "H" Antigen and Human Erythrocytes by the Sera of Patients Treated with ACTH or Cortisone

PATIENT NO.	BLOOD TYPE	TREATMENT			ANTIGEN	DAY AFTER TREATMENT STARTED																						
		Drug	Amt.	Days		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
2	B	ACTH	181	8	RBC	16								16																			
					Typh.	80	40									80																	
3	A	ACTH	386	10	RBC	16										16																	
4	A	ACTH	720	16	RBC	64								64								64											
					Typh.	160								80								20											
5	O	ACTH	557	21	RBC	4							8														16					
					Typh.	20							10														<10					
6	B	ACTH	570	10	RBC	4					16			16								4										
7	O	ACTH	580	18	RBC						32													128								
					Typh.						40		40											40								
8	B	ACTH	690	16	RBC	32					32					32						32										
12	O	Cort.	800–800	7–7	RBC	16					64	64					32										64				32	
13	A	Cort.	900	8	RBC	8			8	16				32			32									32			16			
					Typh.	10			10	10							20									20						
14	A	Cort.		14	RBC	32				32	32	64	32																			
15	O	Cort.	900	8	RBC	64				64		64	64	64								64										

dermal sensitivity of 20 patients to the pneumococcal capsular polysaccharides (SSS) was tested by the method described above. Eight of these patients were given ACTH and 3 others cortisone during all or part of the period between vaccination and testing. There were 9 control patients who did not receive any ACTH or cortisone. Each skin

TABLE V

Changes in Serum Globulin and Antibody in Patients Treated with ACTH

PATIENT NO.	TREATMENT BETWEEN TESTS			ANTIBODY			GLOBULIN (KUNKEL UNITS)		
	Drug	Dose, mg.	Days	Days after Vaccination	Pre-vaccination Titer*	Post-vaccination Rise	Pre-Treatment	Post-Treatment	Change
1	ACTH	2035	19	17	1	6	11	3	−8
2	ACTH	181	7	15	1	0	9	8	−1
3	ACTH	426	15	14	1	6	4	2	−2
4	ACTH	720	16	15	1	6	2	2	0
5	ACTH	557	21	20	1	5	5	3	−2
6	ACTH	570	10+7†	15	0	3	6	1	−5
7	ACTH	580	18	17	0	6	23	22	−1
8	ACTH	690	16	17	0	2	44	27	−17
9	ACTH	570	10	14	1	6	17	18	+1
10	ACTH	781	14	12	0	2	5	12	+7
11	ACTH	668	9	6	0	1	3	2	−1
47	ACTH	570	10	6	4	3	19	1	−18
48	ACTH	480	11	13	3	3	17	14	−3
49	ACTH	200	2	6	2	4	14	10	−4
50	ACTH	1600	11	11	3	0	24	21	−3
51	ACTH	595	11	11	3	2	5	9	+4
52	ACTH	650	13	13	6	0	4	1	−3
Average.....					+3.2			−3.2	

* Titer is expressed as the log of the number of MLD's neutralized by 0.05 ml. of serum.

† Signifies 10 days of treatment followed by 7 without treatment before second tests were made.

site was observed at 30 minutes after inoculation and the extent of the reaction estimated by measuring the diameter of any wheal or erythema. The results of these observations, together with the mouse protective antibody titer of the patients' serum against pneumococcus type II at or shortly before the time of skin testing, are recorded in Table VIII. It will be seen that 3 of the control patients (No. 23, 24,

and 28) had no detectable serum antibody at the time of testing. One of these patients had no demonstrable skin sensitivity; one reacted with erythema but no wheal, and the third with both wheal and erythema. The other 6 patients, with demonstrable serum antibody, all developed skin reactions of varying intensity. It should be pointed out that the skin test material contained the polysaccharides of 6 types of pneumococci whereas antibody was measured against only

TABLE VI

Changes in Serum Globulin and Antibody in Patients Treated with Cortisone

PATIENT NO.	TREATMENT BETWEEN TESTS			ANTIBODY			GLOBULIN (KUNKEL UNITS)		
	Drug	Dose, mg.	Days	Days after Vaccination	Pre-vaccination Titer*	Post-vaccination Rise	Pre-treatment	Post-Treatment	Change
12	Cort.	800	6+6†	15	1	6	3	1	−2
13	Cort.	900	8+5	15	0	6	6	3	−3
14	Cort.	1285	8	7	0	6	8	5	−3
15	Cort.	900	8+7	14	1	5	5	20	+15
16	Cort.	1200	12+2	15	0	5	17	50	+33
17	Cort.	1355	15	13	1	5	4	4	0
18	Cort.	2421	15+1	14	0	4	4	6	+2
19	Cort.	2000	9	8	0	5	8	5	−3
20	Cort.	1795	18+4	17	0	4	12	34	+22
21	Cort.	1720	12+8	18	0	3	15	4	−11
22	Cort.	800	8	8	0	4	14	13	−1
53	Cort.	1050	9	7	3	1	2	2	0
Average.....						+4.8			+4.4

* Titer is expressed as the log of the number of MLD's neutralized by .05 ml. of serum.

† Signifies 6 days of treatment followed by 6 without treatment before second test was made.

type II. Therefore, the absence of dermal sensitivity should not be correlated with absence of antibody.

All of the treated patients had demonstrable serum antibody. However, 3 of the group (No. 7, 9, and 49), all treated with ACTH, showed no dermal sensitivity despite neutralizing antibody titers of 7, 6, and 6 logs, respectively. Except for the suppressed reaction in these 3 patients who might have been expected to react to intradermal polysaccharide, little difference was noted between the treated and control groups.

TABLE VII

Changes in Serum Globulin and Antibody in 30 Control Patients

PATIENT NO.	TIME BETWEEN TESTS, DAYS	ANTIBODY		GLOBULIN (KUNKEL UNITS)		
		Pre-vaccination Titer	Post-vaccination Rise	Pre-Treatment	Post-Treatment	Change
23	17	1	0	3	4	+1
24	17	1	0	13	5	−8
25	17	1	2	15	9	−6
26	14	1	0	9	9	0
27	17	1	5	14	17	+3
28	17	1	0	13	15	+2
29	13	0	3	17	15	−2
30	11	1	4	13	12	−1
31	11	0	6	4	6	+2
32	11	1	5	17	17	0
33	11	1	0	9	8	−1
34	11	1	4	15	18	+3
35	11	1	2	22	19	−4
36	8	0	4	2	9	+7
37	17	0	4	2	15	+13
38	9	0	4	7	10	+3
39	17	0	4	10	14	+4
40	17	1	2	9	20	+11
41	17	1	6	2	11	+9
42	18	1	4	1	1	0
43	14	0	4	4	4	0
44	14	0	4	8	8	0
45	14	0	5	3	3	0
46	14	0	5	7	7	0
54	17	2	3	3	7	+4
55	17	2	4	20	22	+2
56	17	3	4	10	15	+5
57	17	2	5	6	13	+7
58	14	3	3	4	4	0
59	14	4	1	3	3	0
Average			+3.2			+1.8

The average wheal diameter was 6.5 mm. in the former and 7.1 mm. in the latter. The average diameter of erythema was 14.3 mm. in the treated patients as compared with 24.1 mm. in the controls.

DISCUSSION

It has been demonstrated above that in the majority of chronically ill patients treated with ACTH and in about half those treated with

cortisone, there was a fall in serum globulin. This finding is in agreement with other workers (3–7). Concomitantly, somewhat larger amounts of antibody were formed by treated than by control patients. Since the two groups are not entirely comparable as to age and sex, and since the patients in the two groups suffered from different diseases it is impossible to be certain that the observed differences in antibody

TABLE VIII

Dermal Sensitivity to Pneumococcal Polysaccharides

TREATED PATIENTS							CONTROL PATIENTS				
No.	Treatment		Day after vaccination	Antibody titer vs. Pn. II†	Reaction—30 min.		No.	Day after vaccination	Antibody titer vs. Pn II	Reaction—30 min.	
	Drug	Day			Wheal, mm.	Erythema, mm.				Wheal, mm.	Erythema, mm.
1	ACTH	15	13	7	15	20	23	22	0	17	40
7	ACTH	24+7‡	30	7	0	0	24	22	0	0	0
8	ACTH	14	15	2	15	35	25	22	3	5	30
9	ACTH	10+2	16	6	0	0	26	22	1	11	25
11	ACTH	19	16	1	5	7	28*	22	0	0	20
48	ACTH	7	9	6	5	25	29	22	3	5	12
49	ACTH	6	10	6	0	0	30	22	5	12	30
52	ACTH	10	9	6	8	30	54	22	5	12	60
12	Cort.	10	28	6	8	10	55*	22	6	7	0
13	Cort.	9	26	6	15	20					
17	Cort.	14	11	6	0	10					
Average			17.1	5.4	6.5	14.3		22	2.5	7.1	24.1

* Marked local reactions took place 4 hr. after testing.

† Titer is expressed as the log of the number of MLD's of Pneumococcus Type II neutralized by 0.05 ml. of serum.

‡ Signifies 24 days of treatment and 7 without treatment before the test was made.

production were not influenced by some other factors besides treatment with ACTH or cortisone.

In two of these same patients the titer of previously existing antibody (typhoid "H" agglutinins) was lower during treatment with ACTH. It is of interest that McEwen et al. (4) noted a decrease in antistreptolysin O titer in 2 of 3 patients with rheumatic fever during treatment with cortisone and ACTH. In about half of our patients tested, the titer of isohemagglutinins for erythrocytes of another blood group was slightly higher during treatment with ACTH or cortisone.

It is suggested that treatment with these drugs may result in enhanced antibody formation in the presence of a persisting antigenic stimulus, such as that afforded by pneumococcal polysaccharide (10) or under the influence of the continuous control mechanism which governs isohemagglutinin production. However, when the antigenic stimulus is not persistent, as in the case of previous exposure to typhoid bacilli or streptococci, the result of ACTH or cortisone treatment over a period of time may be a fall in antibody titer.

It has been customary to blame the divergent and apparently conflicting results which have been reported concerning adrenal effects on plasma proteins and antibodies in experimental animals on technically deficient experimentation. However, little disagreement exists if the different species are considered separately.

The rat seems to respond in a manner similar to man. White and Dougherty (18) noted an increase in the total serum protein of immune rats 3–6 hours after the injection of ACTH. However, Eisen et al. (23) and Li and Reinhardt (19) found no change in the total plasma proteins of this species. The latter workers reported a rise in the albumin and a reciprocal fall in the gamma globulin fractions after repeated injections of ACTH. Massell, Warren and Sturgis (45) have reported a fall in the antistreptolysin titer in treated rats. The development of agglutinins (20, 22, 23), hemolysins (21, 23, 24, 25) or precipitins (23) have been measured. The differences in titers between experimental and control animals have not been great but the trend has been quite consistent. Eisen et al (23) found no difference in the capacity of adrenalectomized rats to form agglutinins or hemolysins as compared with normal controls but demonstrated a suppression in precipitin formation by the operated animals which was "probably significant". With but one exception (20) all workers have reported that adrenalectomy suppresses antibody formation (21–23) whereas adrenal stimulation or treatment with cortisone enhances antibody production or release (24, 25).

In cats and dogs (26, 27) adrenalectomy resulted in changes in the plasma proteins similar to those noted in human beings with Addison's disease (1). There was a decrease in albumin and an increase in globulin with a reversal of the A/G ratio. However, Hektoen and Curtis (28) reported that adrenalectomy did not affect the antibody titer of

immune dogs and Thatcher et al. (29) found that this operation did not affect the ability of cats to synthesize antibody.

In the rabbit, most workers have reported findings directly contrary to those in man and the rat. White and Dougherty (18) reported a 24 hour rise in total serum globulin and antibody to follow an injection of ACTH into immune rabbits. However, de Vries (30) and Fischel, LeMay and Kabat (31) were unable to demonstrate an immediate effect of ACTH on pre-existing antibody levels in this species. There is general agreement that immunization following adrenalectomy in this species results in enhanced antibody production (32, 33) whereas adrenal stimulation or cortisone treatment during immunization depresses this function (34, 35).

Experiments in mice and guinea pigs have been limited. White and Dougherty (18) have reported a decrease in total plasma proteins in adrenalectomized mice and an increase in those receiving ACTH. Chase, White, and Dougherty (25) found an increase in the level of antibody in previously immunized mice shortly following an injection of ACTH. Vollmer and Samsell (36), however, found no difference from controls in the acquired resistance to pneumococcal infection in mice given ACE throughout the period of immunization. The only published study in guinea pigs is that of Gates (37) in 1918, who found that partial adrenalectomy produced no change in the ability of this species to synthesize antibody.

In summary, most workers have noted similar changes under conditions of adrenal deficiency or stimulation in the plasma proteins of man, rats, cats, and dogs. Moreover, in the rat, like man, there may be a fall in antistreptolysin titer following ACTH treatment; slightly enhanced antibody production may result from adrenal stimulation and adrenal deficiency seems to have a suppressing effect. In the rabbit, on the other hand, antibody production seems to be inversely proportional to adrenal activity. The studies in mice and guinea pigs are too limited, at this time, to classify their response in the respect.

Our observation that dermal sensitivity of the immediate type may be suppressed in some human beings under treatment with ACTH is in agreement with others (38), although Long and Favour (46) did not observe any effect of this drug on histamine sensitivity in man. Moreover, Long and Favour (46), Carey et al. (38),, and Woods (39)

have reported that the delayed type of bacterial sensitivity in human beings is suppressed during treatment with ACTH or cortisone. Tuberculin and bacterial sensitivity in rabbits (34, 39) and guinea pigs (34) is suppressed during treatment with cortisone, despite the fact that neither active nor passive anaphylaxis in the latter species is blocked (40–44). Fischel (41) and Harris and Harris (34) did not observe any blocking of the Arthus reaction in rabbits receiving ACTH or cortisone, but Germuth and Ottinger (35) have reported that the active Arthus reaction in rabbits is suppressed by treatment with these drugs. They presented evidence suggesting that this might be related to impaired antibody production. It is apparent that such an explanation cannot fit the findings in human beings. The present evidence suggests that the beneficial effects of ACTH and cortisone in treating hypersensitivity states and related diseases in man are not to be explained by suppressed antibody production. There may be some interference between the reaction of antigen and antibody in the host but, more likely, interference at some subsequent point in the chain of reactions involved.

SUMMARY AND CONCLUSIONS

1. Fifty-nine patients were vaccinated with pneumococcal capsular polysaccharides. The production of mouse protective antibody during treatment with ACTH in 17 cases and during treatment with cortisone in 12 cases was compared with 30 controls. Antibody production was not depressed by treatment but seemed to be slightly enhanced.

2. Serum globulin, measured by Zn Sulfate turbidity, decreased in 13 of 17 patients during treatment with ACTH and in 6 of 12 patients treated with cortisone.

3. Agglutinins for typhoid bacilli were lower by 4 to 8-fold in 2 of 5 patients and isohemagglutinins were 4-fold higher in 4 of 11 patients during treatment with ACTH or cortisone.

4. The average dermal reactivity to pneumococcal polysaccharides was not depressed in 11 patients treated with ACTH or cortisone as compared with 9 control patients. However, 3 patients treated with ACTH showed no dermal sensitivity despite abundant circulating antibody.

5. The results reported by other workers suggest that there is a

species difference in adrenal effects on plasma proteins and antibody formation. The rat in these respects seems to resemble man more closely than the rabbit.

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THE SIGNIFICANCE OF PERSONAL PROBLEMS IN THE UNDERSTANDING AND TREATMENT OF ILLNESS*

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A good many years of hospital medical practice served to convince me that the consideration of the personal problems of patients as a component of illness is of much importance in the practice of medicine. The clinical study of disease is the essence of modern medicine, and is carried out systematically with ever advancing thoroughness and thoughtfulness in our best hospitals. On the other hand, the routine study of the personal problems of patients, which so often reveals the true nature of their illness, has been haphazard, unsystematic, often unrecorded and frequently neglected in modern hospital practice.

It was with this idea in mind that the systematic study of the patient as a person was undertaken in the Johns Hopkins Hospital a number of years ago and served as the basis for teaching the social aspects of medicine in the medical school. These studies were carried on for over five years, and were terminated at the onset of World War II. During this time hundreds of patients were studied to determine the nature and frequency of personal problems and their relation to illness.

The studies were concerned with illness or ill health, which may be defined as the complaints or symptoms that are recognized subjectively by patients as discomforts, pain or disabilities which restrict their normal living, make them unhappy, diminish their working capacity or cause worry, anxiety and fear. These characteristics of illness are the usual reasons why people seek medical care, and from which they want relief.

Illness may or may not be caused by organic disease, but it was constantly borne in mind during these studies that it is the primary obligation of the doctor to determine by careful clinical studies the existence of organic disease as a cause of illness or of potential ill health.

While illness is determined subjectively by the patient, who is able to describe his symptoms and complaints, the existence of organic disease is determined objectively by physical and laboratory examinations

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and by various tests and measurements conducted or directed by the doctor who evaluates their significance to make a diagnosis of disease. The practice of medicine should be largely concerned with the evaluation of the relation of disease to illness, and with seeking causes of illness that are not to be found by physical and chemical methods.

Our studies were carried on by methods that may be broadly designated as biological. These methods have been described in detail elsewhere,[1] and only the essential features will be recounted. Whatever we learned about the personal problems of patients has come from their own accounts of the circumstances of their lives and from observing their behavior in the hospital and in their homes, often supplemented by statements of those closely associated with them.

Most of the patients that were studied had been admitted to the medical clinics of the Out-patient Department and had had careful clinical study before they were first interviewed. The medical records were reviewed and abstracted beforehand, so that the medical history and physical status of the patients as revealed by their examinations were known. The patients were seen in a quiet office, somewhat removed from the activities of the clinics, and the initial effort to establish a satisfactory confidential doctor-patient relationship was to review with the patients the main points of their clinical records and to find out what they understood regarding the significance of their symptoms.

There are two sides to the doctor-patient relationship. Not only must the patient feel confident of the doctor's desire and ability to help him, but the doctor must feel a sincere interest in the patient as a person and in his problems. This interest must be sufficiently deep to be sustained over long periods and to create a determination to see the patient through his troubles without passing judgment or feeling resentment in regard to behavior involving ethical or moral questions, and without being disturbed by unattractive traits of personality.

Patients were encouraged to give their social history with emphasis on episodes or conditions in their lives that they associated particularly with their illness. During the first or second interview, when the patients were given the opportunity to talk freely to an attentive and interested listener, the reasons for a visit to their homes were usually discussed. Home visits were made in the majority of the cases, and

they were arranged preferably for a time when other members of the household were present, in order to observe the patients in their usual social setting.

Conferences were held frequently with the physicians of the patients in the hospital, occasionally with private physicians who had given them medical care, with social workers within the hospital and in various public and voluntary agencies, public health nurses, ministers, priests and school teachers who had rendered service to them. Full notes were dictated on all interviews, visits and conferences as soon as possible, and records were built up which were not only essential in following the course of each patient, but also in collecting data for analysis and group study.

Social and emotional problems were analyzed and discussed with the patients, and as soon as a clear conception of their personal problems was obtained, efforts were made to give the patients a rational understanding of their problems and of their relation to the symptoms of which they complained. The primary objective was frequently to persuade them to use rational thinking rather than emotional feeling. In other words, patients were encouraged toward emotional maturity, to use a phrase which is popular today, in the consideration of their problems and their illness.

Whenever patients had disturbances which could not be reached and favorably influenced by this simple formula, psychiatric advice and treatment were sought for them. This, however, rarely occurred in the types of patients that were studied.

A particularly useful feature of the study of many of the patients was its duration. Successful efforts were made to keep in touch with them for months or years, by having them return for interviews, by home visits or by letter, in order to gain a long view of changes that may have occurred in their health and in their mode of living. Efforts were always made to establish and maintain the relationship of the family physician and advisor. This was often appreciated by the patients, who seemed to have no one else to advise them about their health, and their personal problems, although expert advice was available regarding the disease from which they might be suffering.

Our studies were carried on with the assistance of a medical social worker and a secretary. The Eastern Health District of the Baltimore

City Health Department was considered to be a favorable area for social studies, as it surrounded the Johns Hopkins Hospital and was a field of study of the School of Hygiene and Public Health. At the suggestion of my wife, we decided to live in the district, and did so during the first three years of the study. This proved to be highly advantageous, as it facilitated home visiting, especially in the evenings, and made it convenient for patients and their relatives to come to our home out of hours for intimate, unhurried talks.

A pilot study of ten dispensary patients living in the district was made, in order to learn how to proceed and how to meet technical problems. These cases, selected at random, were studied quite thoroughly, and revealed much that was instructive and interesting. From one of these patients we learned a valuable lesson.

A woman of 56, who worked in the laundry of the hospital, had poor vision and a continuous hoarseness of voice. She often became excited and very nervous at her work, and she said she was quite "unhappy" and had a sense of dread on going to work, and had shortness of breath on walking upgrade. Her physical examination showed a definitely elevated blood pressure, the systolic pressure being around 230 m.m. Hg and the diastolic pressure 130 m.m. She had evidence of hyperthyroidism, and her basal metabolic rates were plus 30 and 45 on two occasions. A diagnosis of arteriosclerosis was made. The evident emotional tension, and her physical findings, led her physician to conclude that the patient was threatened with cardiac failure, and a change of occupation and more rest were advised.

An investigation of the working conditions of the patient by a visit to the hospital laundry revealed that she supervised four young, inattentive girls and had constant difficulty in keeping them at work feeding clothes into a large ironing machine. It was noticed that one person worked rather quietly alone behind the machine sorting laundry as it came through. It was arranged with the patient and the superintendent to have her changed from the job in front, where her personal relationships were disturbing, to the unharrassing job behind the machine.

A week after the change of job, which the patient did not want to make because it meant a reduction of pay, she said with enthusiasm, "a miracle has happened and a big burden has been lifted from me."

The feeling of excitement was gone, her neck no longer swelled and she was no longer nervous or short of breath.

The patient was followed for several years and had no return of her symptoms. She continued to speak of the effects of her change of work as a miracle, and continued to work steadily without drugs. She gained weight and gave the impression of being a happy, contented person. Her basal metabolic rate dropped to plus 4, but her blood-pressure showed no appreciable change throughout the long period of observation, and 15 months after she was first seen, it was appreciably higher than initially.

In this case a skillful, experienced physician attributed the patient's illness to her organic disease, which was apparently entirely justified, until it was found that the symptoms constituting her illness were completely cleared up by the solution of her personal problem consisting of daily harassing personal relations while at work. The organic disease was unaltered, but was evidently not the cause of the patient's illness for which she wanted relief. Her illness was cured. Her disease persisted.

A systematic study was then undertaken of all the patients living in the Eastern Health District, without selection, who were admitted to the medical clinics of the Out-patient Department and without taking into account any medical data. For about a year as many of these patients as could be reached were interviewed and followed.

A group of 174 cases was studied and their records analyzed. A few patients, who lived outside the District, were seen on the medical wards but otherwise the study was confined to the "run of the mine" of East Baltimore people who sought medical care in the medical service of the Out-patient Department. There were 44 patients with respiratory diseases, including 16 cases of pulmonary tuberculosis, 33 with cardiovascular diseases, a smaller number of patients with gastro-intestinal disorders, syphilis, diabetes and epilepsy, and, there were 45 patients, or 26% of the group, who were diagnosed as having a psychoneurosis and 27 with various other diagnoses.

The study of these patients has been reported in detail.[1] It revealed that 140, or 80% of the group, had personal problems that could be defined and classified. In 115 cases, or 66% of the group, these problems were definitely related to their illness, either as a cause of symptoms, or as an obstacle to the medical care they needed.

The types of personal problems were classified by dividing them into two categories, the first being disturbance of subsistence, consisting of subnormal living conditions, relative destitution, faulty habits and personal inadequancy; the second being personal dissatisfactions connected with either family group relationships or with social life. The first were the external problems and the second, the internal problems of the patients. Seventy per cent of the entire group had disturbances of subsistence, 50% had dissatisfactions and 39% had disturbances of both subsistence and satisfaction. It should be said that these studies were made in 1936 to 1938, a time when there was severe economic depression.

This study gave clear evidence of the frequency and nature of the personal problems of people living in Baltimore who seek medical care from the Johns Hopkins Hospital. Personal problems, such as those encountered in our patients, create emotional stress and strain which disturb bodily functions and so generate a variety of symptoms. The study of this chain of events has recently been designated as psychosomatic medicine. Our study indicates that a large proportion of cases of illness have a so-called psychosomatic component, which should be given consideration by all doctors in all cases. Psychosomatic medicine should not be considered a specialty.

People differ widely in their sensitiveness and susceptibility to their personal problems and for that reason, it is essential to evaluate the personality of patients as well as the problems that confront them. It is in this domain that the family doctor who used to practice in the home of his patients had such an advantage over those who practice in these days of specialism, office visits, clinics, hospitals and medical mass production.

The advantages of visits to the homes of patients has recently been emphasized by the Chairman of the Section on General Practice of the American Medical Association, Dr. Milton Buford Casebolt, in his Chairman's address at the 1950 annual meeting of the A.M.A.[2] He said, "I maintain that in many instances intelligent diagnosis cannot be made unless the physician visits the home of the patient. The system of strictly office and hospital medical practice leaves much out of the picture on which the physician might base a diagnosis of many ailments." It is his conviction that the physician cannot know the full story unless he knows the home and family life of the patient.

It was because our studies soon brought us to similar conclusions that home visits, preferably when the families of patients were there, were made routinely whenever possible, and in some instances repeatedly. Visits were made to the homes of 111 of the 174 patients in this group, and afforded valuable opportunities to observe their social situations, living conditions and family relationships, and gave us a clearer conception of their personalities than could be obtained at the hospital.

How a home visit may reveal personal problems that cause illness and create an obstacle to adequate medical care is well illustrated by the case of the Negro woman who had a fairly severe anemia of secondary type and who was instructed to rest at home and to take a prescribed diet detailed on a list that was given to her. In order to see how well the patient could carry out these instructions, she was visited at home with the student to whose care she had been assigned in the Dispensary.

The visit was made at the end of a cold winter day. The patient's husband opened the door and politely asked us to go upstairs to see his wife who was with the children in the only heated room in the house. There, we were confronted with a surprising sight. We found the patient with her thirteen children, the oldest sixteen and the youngest a baby being fed oatmeal water in place of milk from a bottle. The children were neatly dressed, quiet and well behaved, and were lined up on two benches along the walls or sat on the large bed in the middle of the room. When a census was taken, we found that the patient had had a baby in each calendar year except two, for fifteen years, and that none of them had died. Her mother, she said, was a professional midwife.

The husband had a W.P.A. job, which meant that he was employed on work provided by the Government to meet the strain of the depression years, and was receiving $49.50 a month, the wage that was supposed at least to prevent starvation. As the husband was employed, the family was not eligible for public relief. It required only a glance to see how well the instructions of rest and a prescribed diet for anemia could be carried out in this household.

Food was obtained for this family the next day, partly by the donation of sample foods from the supply of the Dispensary dietition and other emergency arrangements were made, including referral of the

patient to the Planned Parenthood Clinic, which she subsequently attended.

About two weeks later the husband appeared in the Dispensary with pleurisy which prevented him from working and made him eligible for public relief amounting, with Aid for Dependent Children, to over $100.00 a month. When the husband was seen at the hospital three weeks later, and asked how he was, he replied, "I'm still sick, thank God."

With proper nourishment the patient made a good recovery, but the last news of her was that she had had another baby. This case is a good example of those classified as disturbances of subsistence.

The value of a home visit in a case classified as dissatisfaction is illustrated by a 27 year old man who operated an overhead travelling crane in a steel mill. He had had abdominal pain and a "lump in his throat" for a year; had lost 24 pounds and said he had lived on medicine bottles for six months. No physical causes for his symptoms were discovered, and he thought his job was at fault as he sat alone at work and was annoyed by the orders shouted or signalled up to him from below.

A visit to his home showed that he and his attractive red-headed wife argued, disagreed and nagged at one another, and there was evidently considerable emotional friction between them. When it was proposed to him, on his next visit to the hospital, that his underlying difficulty was his ill-temper toward his wife and his hours of rumination over their disagreements while at work, he readily agreed that this was probably true. He was given some homely advice, which he said he would try to put into practice, and was told that it was up to him to cure himself. He succeeded, and several years later he reported that he had not had a day of illness or discomfort since he had begun to put into practice this advice which, he declared, had saved his life.

The study of this group of unselected patients gave convincing evidence that consideration of the personal problems of patients was often essential for a correct diagnosis and for effective treatment of their illness. Psychogenic symptoms often confused the clinical picture of organic disease, and the illness of some patients was not fully understood because their emotional disturbances had not been given adequate consideration by their physicians.

In the following case a comprehensive study of the patient brought

about an important change in the diagnosis and gave him a much more favorable outlook on life. A 34 year old industrial worker who came to the hospital complaining of a cold, cough, and shortness of breath had signs of bronchitis, tonsillitis and a well-defined mitral systolic heart murmur. He had had rheumatic fever at the age of 12, and was informed that he had rheumatic heart disease with a mild degree of cardiac failure. His tonsils were removed and he was treated for his heart failure.

During an interview he related that two years previously he had been injured in an automobile accident, and had spent thirteen very disturbing weeks in a hospital. On his discharge his doctor told him that because he had heart disease he should avoid physical exertion. Since then he had been an invalid, and on visiting his home, it was found that he was spending much of his time in bed, living on public relief with his wife and two children in a poorly lighted, low rent first floor apartment.

When his history was obtained in greater detail, he said that, although at the age of 19 he had been told he had a heart murmur, he had done strenuous work in a steel mill, had worked as a furniture mover, and had gone through military maneuvers as a member of the National Guard without untoward symptoms.

A more careful analysis of his symptoms indicated that they were not typical of cardiac failure, but were indicative of a post-traumatic neurosis, complicated temporarily by an upper respiratory infection. He was, therefore, encouraged and persuaded that he was capable of leading an active life. He was given assistance and advice in getting a chauffeur's license and a job in a garage. He thus became a self-supporting, self-respecting man with a sense of liberation, and was able to carry on his work without discomfort or physical limitations.

There were many patients in our series for whom their personal study and simple psychotherapy, combined with their clinical study were a major factor in their recovery. Much was accomplished with the 45 patients diagnosed as having psychoneuroses. Some with illness of many years' standing became symptom-free and were able to lead normal lives in comfort with satisfaction.

The success of the treatment of many of these patients was brought

about by investigating more carefully their personal problems than was customary in the medical service of the hospital, and in making greater efforts to adjust the circumstances of their lives.

An example of such treatment is the case of a sixteen year old high school girl who had suffered from headaches, fatigue, drowsiness and back pain for about four months which had interfered with her school work so much that she was failing in her studies and her forced withdrawal from school was threatened. No physical abnormalities to explain her symptoms were found, but she showed evidence of distress when her school work was discussed. The harshness of her father regarding her school difficulties was a large factor in her emotional strain.

A conference with the principal of the school and with the school nurse confirmed the seriousness of this girl's problem, and they agreed to a suggested transferral to a vocational school, rather than have her fail in the coming examinations and be eliminated from further public school opportunities. This was then taken up with the principal of the vocational school and with the father of the patient. The latter, after a long talk one evening, was made to see how detrimental was his attitude toward his daughter. The vocational school principal became much interested in the therapeutic plan and finally both of them cooperated fully in helping to achieve a very successful adjustment. The patient was changed from a situation which seemed to be endangering her future health and perhaps her mind, as she showed personality characteristics suggestive of early symptoms of schizophrenia.

She became a happy, successful student being trained in tea-room management and during the next year or so was entirely well and happy. There was definite improvement in the family life, which had previously been strained and uncomfortable for all of its four members.

Our next study was a group of patients admitted to the Gastroenterological Out-patient Clinic. Dr. Moses Paulson, Assistant Professor of Medicine and physician in this clinic, was much interested in this study and agreed to refer all patients assigned to him for interviews and personal analysis, after the clinical examinations were completed. The clinical and personal studies were closely correlated by

frequent conferences and were combined in the diagnosis and treatment of patients. A series of fifty patients was studied by the methods that have been discussed, and a report has been published.[3]

In this series, there were 38 patients, or 76% of the group, who had emotional or mental disturbances which were considered to be the cause of their illness. There were only six patients with demonstrable lesions of the gastro-intestinal tract, and only 13 that required treatment by the special methods of the gastro-enterologist.

The personal problems in this group of patients were almost exclusively disturbances of satisfaction or internal conflicts, and were designated in this study as "personality disorders." They were classified, with the advice of the psychiatrist, Dr. Thomas A. C. Rennie, as follows:

Excessive emotional reactions	15
Hypochondriacal reactions	13
General or constitutional nervousness	4
Depressions	3
Hysterical reactions	2
Anxiety attacks	1
	38

Twenty-three of these patients responded favorably, some of them almost immediately, to our simple form of psychotherapy, while 15 did not. Nearly all of those with excessive emotional and hypochondriacal reactions responded very favorably, while those with general or constitutional nervousness, hysterical reactions and depression did not. Several of them were referred for psychiatric treatment.

The patients who responded favorably were those to whom an understanding of their problems could be given, and who could be persuaded to change their attitude toward their illness and alter their habits of thought. The one patient with anxiety attacks made a remarkable recovery when he came to understand his complicated situation, which may be briefly told.

He was a young baker, 21 years old, who had been married for 17 months, at which time he began to have attacks of severe choking sensations, difficulty in breathing and cardiac palpitation, especially when he attempted to eat. These symptoms had become gradually

worse as the time approached for his wife to have a baby. No physical cause for his symptoms could be found.

During the interview after much hesitation and reluctance, he said he feared tuberculosis, and told how he had watched an older friend who lived next door and whom he greatly admired, go slowly down hill with tuberculosis and finally die at the time his wife had a baby. The patient's mother had used this episode to try to enforce early hours and good behavior on her son by telling him quite often that if he did not stop playing the saxophone in a dance orchestra, which kept him out late and which was his chief source of pleasure, he too would get tuberculosis and die, as his friend had done. She succeeded in planting this idea in his mind, which blossomed forth as severe anxiety attacks, making his life very unhappy and rendering him unable to work.

The patient was greatly relieved by the assurance that he had no evidence of tuberculosis. His symptoms disappeared entirely after the baby was born a few days later and after a visit to his home where his mother was admonished in his presence never to mention tuberculosis again. Two weeks later he reported that all his symptoms had disappeared, he could now eat without discomfort and that his wife and baby were doing very well. He had returned to work and was a very happy and greatly changed young man.

An example of how a hypochondriacal reaction can be dispelled is the case of a cheerful looking 35 year old housewife, who had had abdominal discomfort and pain for three years, which had been constant for the last year. Clinical studies, including a gastro-intestinal X-ray series, failed to reveal any abnormalities.

She confessed, at her second interview after we were better acquainted, that she thought she had cancer and had made all of her funeral arrangements before coming to the hospital, as she thought, to die. She said her symptoms began at 1:00 P.M. on a Saturday afternoon three years before when she heard the symptoms of cancer of the stomach described over the radio. Since then she had never missed this particular so-called "health broadcast" and had read all she could find regarding health in the newspapers.

She was persuaded to give her thoughts to her garden and chickens in the country where she lived, and to stop ruminating on her death

from cancer, of which she had no signs or symptoms. Three months later she wrote that all of her digestive symptoms had disappeared, although she was very nervous at times, but that our talks had changed her outlook regarding her health, over which she no longer worried.

The study of this group of 50 patients clearly demonstrated the prevalence of the emotional basis for the symptoms of many patients with gastro-intestinal complaints, and the necessity of studying them by methods that reveal their personal problems. It also indicates how important it is to treat these patients by psychotherapy after their problems are clearly understood, if they are to receive adequate medical care.

Let us compare the personal problems in this group of patients with gastro-intestinal symptoms with another group of 50 patients with active pulmonary tuberculosis which we have studied and analyzed. Tubercle bacilli had been demonstrated in 38 cases, or 76% of the patients, and there could be no doubt as to the specific cause of their illness. They had all been diagnosed as moderately or far-advanced pulmonary tuberculosis, nearly all of them resided in the Eastern Health District and, with a few exceptions, were visited at home, sometimes with a public health nurse or with a medical student. All of these patients had personal problems, as the disease itself constantly creates them, but beyond the emotional and social disturbances produced by the disease, there were 28 patients with severe adverse social conditions, disturbances of subsistence, that were obstacles to their home treatment or to their going into a tuberculosis hospital for treatment and isolation. Over-crowded dwellings, especially among the Negro patients who constituted half of the group, were especially disturbing, and many of the patients were destitute.

In one home a patient who died two weeks after our visit was found to be sitting in the only heated room in the home with his mother and sister, 10 children from 15 to 3 years of age, and a visitor who played a guitar in an effort to cheer up the situation. Better conditions for the spread of the disease, and worse conditions for its treatment can hardly be imagined.

It is not necessary to describe the adverse social problems of patients with tuberculosis in the lower economic groups, where the disease most frequently occurs. But it may be said that there were only 5 or 6 patients in this series of 50 who seemed to have a fair chance of re-

gaining and maintaining their health by proper tuberculosis hospital care and by returning to an environment favorable to the prevention of reactivation of their disease.

There are three periods in the course of tuberculosis when patients are frequently in urgent need of professional assistance in meeting their personal problems. This assistance is needed especially to get the patients into tuberculosis hospitals, to keep them there as long as necessary, and to get them out so that they may live as they should in their own homes and communities.

In the first period, consideration must be given to the fact that the diagnosis of tuberculosis has such dreadful implications to many patients that its pronouncement by their doctor often causes serious emotional reactions. Some patients fail to hear or comprehend the explanations and instructions that follow the statement of diagnosis, some patients show deep resentment or refuse to accept the diagnosis, while others concentrate on the serious problems they must face in order to undergo treatment. These mental and emotional reactions and the special preparations that are needed for home treatment and for leaving home to go into a hospital raise serious questions for the physician and for the public health nurse, who need at this time the skillful cooperation of the medical social worker.

The second period covers the time in the hospital, when months of treatment may wear out the courage and persistence of patients who are poorly integrated in their hospital life, or when they are faced with deforming surgical procedures, or when they feel that the home situation demands their presence.

Patients with tuberculosis who need prolonged hospital care require not only encouragement and emotional adjustment to a sort of life that is new to them, but often have families to be left behind, creating problems which can be solved only by constructive planning. This can be properly met only by the study of their individual circumstances. Efforts are being made to meet the problems of these hospitalized patients, not only by the organization of medical social work, but also by the provision of occupational and educational therapy, skillfully operated library services and vocational rehabilitation. The support of religion, through the services of priests, ministers and rabbis is also of much value during this period.

The necessity of professional consideration of the personal problems

of tuberculosis patients has become generally recognized as an essential part of their treatment and as a means of preventing them from leaving the hospital against medical advice.

In the third period, consideration must be given to the fact that discharge from the hospital creates difficulties for patients when they have to face again their family and community situations, generally after a prolonged absence. The attitude and understanding of their families regarding the disease should be investigated and adjusted before the patient is discharged. Thus the patient can live with a minimum of emotional and physical strain until the chance of a recurrence of the disease is lessened, and so that no obstacles exist to prevent the medical follow-up which they must have.

In all three periods there is a great need for medical social service, which at present cannot be given completely and adequately anywhere.

In conclusion, let us say that we believe that our studies give convincing evidence that the study of the personal problems of patients is necessary for the proper understanding and treatment of illness, and that they should be given careful consideration in many types of illness, especially when prolonged and when chronic disease is present. They often produce emotional disturbances that cause not only illness, but also create suffering and disability of patients with organic disease. Adverse social conditions frequently form obstacles to adequate medical care.

If effective study and treatment of personal problems are to be widely utilized in the private practice of medicine and in clinics and in hospitals, a further reorganization of the methods of medical practice is necessary. In this reorganization the medical social worker must have a more prominent place than at present, and be more closely integrated into diagnostic and therapeutic procedures.

Greater emphasis is being given to the consideration of the personal problems of patients with the closer coordination of psychiatry and internal medicine in some of our teaching hospitals. This, no doubt, is impressing medical students with the importance of the study and treatment of such problems in the practice of medicine. If the coming generation of doctors applies and expands this teaching in practice, it will not only greatly improve medical service, but will meet much of the present-day dissatisfaction with the medical service many people now receive, and which is felt quite generally by the public.

I believe that this dissatisfaction is the basic cause of the disagreements and frictions that exist at present between organized medicine and a large section of the public. Many people are searching for medical care to relieve their discomforts, pains and disabilities which restrict normal living and make them unhappy by generating worry, anxiety and fear. Their satisfaction of medical service would be greatly increased if skillful attention were given more often to the study and treatment of their personal problems.

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LIGATION OF THE HEPATIC AND SPLENIC ARTERIES IN THE TREATMENT OF PORTAL HYPERTENSION WITH A REPORT OF SIX CASES

Preliminary Report

WILLIAM F. RIENHOFF, JR.*

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The surgical treatment of portal hypertension due to intrahepatic disease, such as various types of cirrhosis of the liver, has to date been unsatisfactory in many cases. This is so in spite of the great number of interesting and ingenious methods described to decompress the portal bed by short-circuiting procedures. Many and varied have been the methods employed to correct the clinical manifestations of portal venous obstruction, such as bleeding esophageal varices and/or ascites. To name only a few such procedures: the direct cauterization of esophageal varices by the injection of sclerosing solutions; resection of the lower end of the esophagus; ligation of the splenic artery with or without splenectomy; creation of a by-pass between portal and systemic circulations such as spleno-renal or porto-caval shunts; omentopoexy (Talma operation) have all raised the hope that a definitive solution of this problem had been accomplished. For many reasons these procedures have failed, not the least of which in some of the critically ill patients, have been the insurmountable technical difficulties. In spite of a great number of ingenious methods for the alleviation of ascites none has proved successful in a great majority of the patients treated.

It is the object of this preliminary report to call attention for the first time to a much more simple method of lowering the pressure within the portal vein, and to report its successful clinical application in a series of six patients with Laennec cirrhosis of the liver.

The first patient so treated, whose chief clinical manifestation of portal hypertension was ascites; and the sixth, in whom exsanguinating hemorrhages from esophageal varices associated with cirrhosis of the liver without ascites, will be described in detail.

* Discussion paper by Howard K. Gray and Frank B. Whitesell, "Hemorrhage from Esophageal Varices." Transactions of the American Surgical Association, Vol. 68, 1950, page 489.

In this brief report the clinical histories of the remaining four patients similarly and as successfully treated will be noted briefly. In a more complete manuscript to be published later all of the clinical details and illustrations of the operative procedure will be published.

The first patient, in whom the main complaint was ascites, was operated on June 7, 1947, at the South Baltimore General Hospital. The following is an abstract of his history.

Patient: F. H., Age 50, White, Male, admitted to South Baltimore General Hospital June 2, 1947. Discharged June 21, 1947.

Final Diagnosis: Laennec's Cirrhosis. Marked portal hypertension with ascites. Edema of lower extremities.

History: Patient was in the hospital in March, 1947. C. C. Swelling of abdomen and legs. P. I. Patient states he was in good health until about 1–1½ years ago, at which time he had a swelling and weakness of both feet and ankles. Was unable to walk without a cane. About five years ago he developed marked swelling of the abdomen which had gradually become more pronounced. Because of the severe discomfort from the swelling of the abdomen, patient was forced to rest in bed. Until two years ago, he worked as a bartender, has drunk one to three quarts of whiskey per day for at least five years. He was eating very irregularly, often going the entire day with little food. It was necessary to withdraw fluid from his abdomen on a number of occasions in the Out Patient Department before his admission in the hospital. He was given a thorough trial of medicinal therapy, to which he did not respond, and was troubled with ever-increasing ascites, in spite of frequent intravenous injections of vitamins and many abdominal paracentesis. His physical examination, except for a markedly distended abdomen, obviously due to pronounced ascites, was essentially negative.

Operation: The patient was operated on on June 7, 1947, under spinal and pentothal anesthesia, at which time his abdomen was explored and found to be markedly distended and filled with yellowish serous ascitic fluid. Five liters of fluid were removed at the time of operation by aspiration. The liver was very much diminished in size and covered with an icing which resembled the icing on a cake, a whitish, pale yellow capsule. It was extremely firm, increased in consistency, and obviously from the nodular appearance and feel, was a typical periportal or Laennec's cirrhosis. A biopsy was performed and the microscopic examination later showed a typical scarred liver of the Laennec type. At this operation the main hepatic artery was ligated in continuity distal to the departure of the gastro-duodenal artery. The splenic artery was ligated at the point of its departure from the coeliac axis. The abdomen was closed and the patient returned to the ward in excellent condition. This patient had been prepared for a week before operation by intramuscular injections of 600,000 units of penicillin daily, together with 1 gram of streptomycin.

It has been impossible to persuade this patient to come into the hospital for further laboratory studies. It has not been necessary to perform paracentesis on him since his operation. He returned shortly afterwards to his job as bartender, has persisted in drinking beer and, as he states, five to six drinks of whiskey per day. On physical examination there is no evidence of re-accumulation of ascites. The patient looks very well indeed and states that he feels better than he has in years. It has been three and one-half years since his operation was performed.

It was felt at the time the better policy to delay reporting this patient until further data as to the effect of ligation of the hepatic artery were available, and also to have the opportunity of so treating other cases, to prove that survival following ligation of the hepatic artery was not merely coincidental with some possible anomaly of the circulation to the liver.

The second patient, whose clinical course was characterized by extremely severe hemorrhages, was operated on February 11, 1950. The clinical history is as follows:

Patient: J. D., Age 59, White, Male, admitted to Church Home and Hospital February 3, 1950. Discharged March 1, 1950.

Diagnosis: Hematemesis due to esophageal varices and Laennec's cirrhosis.

Complaint: Patient was admitted with a complaint of vomiting blood of seven hours' duration.

Present illness: For the past seven or eight months the patient has had episodes of eructation and generalized abdominal distension. He has had indigestion with a burning sensation in his stomach and a lack of appetite. Occasional colicky pains. Seven hours prior to admission the patient had a sudden attack of nausea and vomited a large amount of coffee ground material. The vomiting continued for almost twenty-four hours and it was estimated that well over a quart of blood had been lost. The only contributory factor in the past history was that the patient consumed quite large quantities of sherry each evening before retiring, sometimes as much as a bottle or more. This was a habit of many years' standing. On the day of admission to the hospital the patient vomited over a liter of bright red blood. He was given daily transfusions of whole blood. The bleeding was apparently stopped but four days after admission the patient was found lying on the floor unconscious in a pool of blood which he had vomited. On February 8th, patient was esophagoscoped by Dr. E. N. Broyles, but the profuse bleeding in the lower end of the esophagus made a positive diagnosis of esophageal varices somewhat uncertain, but Dr. Broyles' impression was that esophageal varices were the source of the

hemorrhages. Blood transfusions were continued and on February 11th the patient was explored under general anesthesia.

Operation: On opening the abdomen the liver appeared to be the site of pronounced cirrhosis of the nodular type. A biopsy of the liver was taken, which proved upon microscopic examination to be the site of Laennec's cirrhosis. At this time the hepatic artery was ligated in continuity distal to the departure of the gastro-duodenal and the splenic artery was ligated at the point of its departure from the coeliac axis.

Very little preoperative laboratory work could be done on this patient because of his severe clinical condition, but for several days he received intravenous injections of 100,000 units of penicillin and one gram of streptomycin each day. This was also carried out during the postoperative period for his entire stay in the hospital. Preoperatively the hemoglobin was 7.8 mgm; red count 2,500,000; blood sugar 80; and N. P. N. 30. Total proteins were 5.17 mgm. Postoperatively the N. P. N. rose to 40; blood sugar 116; and chlorides 356. Patient's postoperative course was uneventful. He had no further hematemesis. He was discharged from the hospital on March 1, 1950, at which time the patient's condition was good. On arriving home he had one slight episode of vomiting blood-tinged fluid. He was re-admitted to the hospital and given a transfusion of whole blood. After this admission to the hospital the patient's hemoglobin rose from 5.8 mgm. to 10.1 mgm. with an N. P. N. of 27 mgm. per cent.

Since the second discharge from the hospital one year ago, the patient has been back at work feeling in the best of health and appearing so. His diet is perfectly normal and he is allowed to drink some beer with his evening meal. He has returned to his occupation, which is that of a medical artist, and has been working full-time for several months. He very kindly consented on July 16, 1950, to be admitted to the Johns Hopkins Hospital for a follow-up study. History 544378.

His clinical history and physical examination on this admission were non-contributory. The pathological diagnosis of the biopsied liver as being that of a typical Laennec's cirrhosis was confirmed. His liver on physical examination could be palpated one to two fingerbreadths below the costal margin. The patient had no complaints whatsoever, and was asymptomatic.

A needle abdominal aortagram was performed by Dr. Robert Sloan of the Dept. of Radiology. The needle was introduced into the abdominal aorta posteriorly, its tip entering the aorta at the level of the interspace between T-12 and L-1. There was a good injection of the superior mesenteric and renal arteries. The main trunk of the coeliac axis was not clearly visualized. The gastro-duodenal artery was well visualized and this vessel and its branches appeared normal. There was no filling of the vessels in the region of the liver. The blood flow through the liver was measured by Dr. Bing by means of catheterization of the hepatic vein and

injection of Bromsulphalein. The flow was 1193 cc of blood per minute. This is at the lower level of flow and is due to the fact that the hepatic artery is not contributing blood to the liver.

The Prothrombin time on this admission was 17 seconds:

R. B. C., million per c.mm., 4.21; hemoglobin, gm. per 100 cc., 10.8 (75%); col. packed R. B. C., cc. per 100 cc., 34.8; W. B. C., 6,200; V. P. W., 0.7; sed. mm. 1 hr. 29, corr. 12; ict. index 4; M. corp. vol., 83; M. corp. Hb., 26; M. corp., Hb. conc., 31; platelets on sm., normal; achromia, slight; polychrom., none seen; nuc R. B. C., none seen; stippling, none seen; anisc., normal; Poikilo., slight; juv. neutro., 2%; eg. neutro, 52%; eosine, 3%; baso, 1%; lymphocytes, 28%; monocytes, 14%.

BLOOD ANALYSIS

S. N. P. N., 22 mgm. %; phosphorus, 4.2 mgm. %; alkaline phosphatase activity 6.0; ceph. floc. +++; thymol turbidity, 6.2 units; total serum protein, 7.5 gm. %; albumin, 4.6 gm. %; globulin, 2.9 gm. %.

This patient was seen today, February 11, 1951, and is in splendid health one year following ligation of the hepatic and splenic arteries.

A third case operated upon by Dr. Cyrus P. Markle, at the West Penn Hospital in Pittsburgh, Pa., on July 14, 1950, at our suggestion, has remained perfectly well. The detailed account of the clinical history will be given in the final report. Suffice it to say the patient was admitted nine times for exsanguinating hemorrhages from esophageal varices. The common hepatic artery was doubly ligated and divided distal to the gastro-duodenal artery. The patient had alcoholic cirrho sis of the liver.

Our three remaining patients were similarly operated upon by Dr. D. M. Lupo for ascites and are at present well.

As stated in the beginning of this report, the object is to add yet another method of reducing portal hypertension which possibly may prove to be of some value in the treatment of patients with intrahepatic diseases, although, of course, it is recognized that this series of cases is far too small to draw sweeping conclusions as to the true worth of ligation of the hepatic artery. However, the simplicity of this procedure recommends itself as one that might be attempted before other more difficult and exhausting operations are contemplated and performed.

It was most interesting to the author, as well as to other members of the surgical staff, that patients with severe cirrhosis of the liver will survive ligation of the main hepatic distal to the gastroduodenal

artery. In two of the cases herein reported the splenic artery as well has been ligated. The rationale of this procedure was based on clinical trial and later more recent experimental evidence to be fully described in the final publication, that the pressure within the portal vein is definitely lowered when the hepatic artery is ligated. Furthermore, this pressure can be still further lowered by ligation of the splenic artery. Approximately 1500 centimeters of blood pass through the liver per minute, or approximately 100 centimeters per 100 grams per minute. Of this 1500 centimeters it has been estimated that the portal vein carries approximately 75 per cent, of which about 30 per cent comes from the spleen. The rationale, therefore, of ligation of the splenic artery is, of course, to diminish the venous return from the splenic vein into the portal. For instance, examination following ligation of the splenic artery for Banti's disease in the past showed the spleen became atrophic and served somewhat in reducing further the portal pressure by virtue of the remaining venous channels to the spleen that were preserved. Approximately 25 per cent of the blood entering the liver is brought to it by the hepatic artery. The pressure in it is about 120 millimeters of mercury and definitely higher than the average pressure in the portal vein, which varies from 8 to 12 millimeters of mercury. In other words, blood reaching the liver from the hepatic artery is under high pressure, whereas that coming in from the portal vein has a much larger volume with a low pressure; that both empty into a common sinusoidal and capillary bed with the same channel of exit through the hepatic vein. There is an equalization of these pressures between the portal vein and hepatic artery at the junction of the inter- and intra-lobular venules of the liver lobules which occurs through the communications between the veins coming from the capillaries bringing arterial blood and the portal venules. Recent experimental work has shown that the rise in portal pressure was 1 millimeter for every 40 millimeters of arterial pressure. In the cirrhotic liver it is 1 millimeter for every 6 millimeters of arterial pressure. Portal vein pressure rises in cirrhosis to levels that are two to three times that of normal (350 to 500 millimeters of water). The fibrotic change in the liver as a result of cirrhosis changes the pathways of blood flow from the more complex tortuous plexuses to the simple reduced and distorted vessels and thus diminishes the blood flow through the liver. Perfusion

experiments have shown that the blood flow through the hepatic artery in cirrhosis encounters less resistance than in the normal liver, and the blood flow in the cirrhotic liver is less than normal. The higher pressure blood flow (through the hepatic artery) with less resistance tends to increase the resistance to the flow through the liver from the portal vein. The rationale of ligation of the common hepatic artery is based upon the fact that lowering the intra-arterial pressure also lowers that in the portal vein. Variations in the origin and distribution of the hepatic artery must be constantly held in mind and in the future arteriograms postoperatively should throw some light on not only the possibility of aberrant hepatic vessels but also on the development of collateral circulation, which at the present time is obscure in the human. Not infrequently the right hepatic artery may rise from the superior mesenteric, from the aorta, from the right renal; and also it is to be noted that there may be an accessory left hepatic artery which arises from the left gastric artery. The ligation in this group of cases, excepting one was done, as stated, in continuity distal to the departure of the gastroduodenal artery.

It is to be noted also that each of these patients received penicillin and streptomycin before and after operation. This is interesting in view of the experimental work published by Ravdin and his co-workers at the University of Pennsylvania, who found that when the hepatic artery in dogs was ligated unless penicillin and streptomycin were administered to the animals, death would occur from anaerobic bacterial infections of the liver. In the earlier cases herein reported, penicillin and streptomycin were administered but at that time the author was unfamiliar with these observations.

Conclusions. Patients with alcoholic or Laennec's cirrhosis have survived ligation of the common hepatic artery distal to the departure of the gastro-duodenal artery along and in conjunction with ligation of the splenic artery. The clinical manifestations of portal hypertension, such as bleeding esophageal varices and/or ascites have apparently been allayed by this surgical procedure. It is not to be presumed that this operation will be successful in all patients in whom it may be used; its success will depend to a large extent on the critical condition of the patient or the advanced stage of the disease. It would seem, however, that it may have a definite place in selected cases. It has

indeed simplicity of performance to recommend it. The patients should be prepared preoperatively by the administration of penicillin and streptomycin. Ligation of the common hepatic artery for traumatic aneurysm has been accomplished in three patients who were cured, with no untoward effects on the liver, as reported by Grant, Fitts and Ravdin (1). Apparently the liver in these patients was undamaged before and after ligation of the hepatic artery. Whether or not the ligation of the common hepatic and the splenic arteries will prove to be a valuable procedure in a larger series of cases remains for the future to decide, but at least it can be stated that patients will survive such a procedure. The hepatic and splenic should always be ligated together in instances of portal hypertension. In severe injuries to the liver perhaps the hepatic artery might be tied for hemorrhage from the liver.

In summary then, the rationale for the ligation of the common hepatic artery alone, and also together with the splenic artery for lowering of portal pressure has been discussed. A report has been made of six cases of Laennec's cirrhosis in which this procedure has been carried out successfully.

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Since this preliminary report went to press, the author has received a communication of a patient with cirrhosis of the liver operated on by Dr. Claude J. Hunt, of Kansas City, Missouri; another by Dr. Paul A. Kunkel, Jr., of Harrisburg, Pennsylvania; and four by Dr. Philip Thorek, Jr., of Chicago, Illinois, bringing the total number of cases to survive this operation to twelve, including our own. A detailed report of the follow-up studies will be given in the final paper.

MEETING OF THE JOHNS HOPKINS MEDICAL SOCIETY

Hurd Hall, Monday, January 8, 1951

Dr. Fisher: I'd like to call the meeting to order. We have a very full program this evening. The first of these interesting papers is by Drs. H. W. Scott, Jr., C. R. Hanlon, and B. J. Olson, and will be given by Dr. Scott.

THE EFFECTS OF EXPERIMENTAL ALTERATION OF THE PULMONARY ARTERIAL CIRCULATION ON TUBERCULOSIS IN MONKEYS

Studies carried out during the last 2½ years by the authors at the National Institutes of Health were reviewed and results illustrated by lantern slides. It was found that anastomosis between systemic and pulmonary arteries in monkeys infected intravenously with human tubercle bacilli results in an extensive caseous form of the disease in the lung on the side of the anastomosis. Subsequent experiments with ligation of a pulmonary artery in similarly infected animals demonstrated that the same type of caseous process develops in the lung on the side of the arterial ligation. In contrast, the lung on the side opposite the ligation or anastomosis shows the miliary form of tuberculosis typically found in both lungs of control animals. More recent studies of the effects of systemic-pulmonary anastomosis under a variety of conditions of exposure to tubercle bacilli have confirmed and extended the original observations. It may be concluded that "arterialization" of the lung or a segment of the lung in monkeys with tuberculosis induced by various modes of exposure results in extensive caseous changes in the arterialized pulmonary tissue. The experiments suggest that the caseous changes are related to high oxygen tension in the blood perfusing the arterialized pulmonary tissue.

Dr. Fisher: Dr. Olson is here from the National Institutes of Health. Would you like to say a word about this, Dr. Olson?

Dr. Olson: Mr. Chairman, Members of the Group: We feel very privileged to have had an opportunity to participate in work with Dr. Scott and Dr. Hanlon. The original concept of the work, and what might be brought forth, is really entirely theirs. We have learned a good deal in participating in these experiments.

As doubtless many of you know, there are fundamental factors back of the evolution of tuberculous lesions. These have been studied and considered for rather a substantial number of years now, with perhaps more being written on the subject than actual light being thrown on what is happening.

One of the interesting things to me in studying the experimental monkeys after this very skilful surgery has been that regardless of the operative procedure used rather consistent results were obtained.

These experiments are time-consuming. One is always faced with an ever-

present problem: Should you carry out the procedure, then sacrifice the animal at the end of six weeks, and deduce the results—see the results which you have—and then deduce what might have happened if the animal lived. It was definitely decided that the opposite course would be taken; namely, these animals would be subjected to this surgery, would be infected under reasonably standardized conditions, as much as you can standardize a culture, and then we would proceed to wait until the animal itself elected to die of the disease. I think that, although the average experiment may take a year and a half to do after initiated, it has proven worthwhile because it has given us a full picture of the evolution of these lesions.

As far as one other point in these experiments is concerned, I would like to emphasize a little more than Dr. Scott that these animals, prior to being studied, were free of tuberculosis. As you know, one of the serious problems with monkeys is that tuberculosis is probably contracted enroute from the tropics, where all are caught in the wild state. I would like to emphasize that these monkeys were clearly free of tuberculosis. The animals used in these experiments were found to have a negative tuberculin, and were negative to tuberculosis by any test we knew. Then, in addition, most of them were held in isolation for six months to make absolutely sure there wasn't a stray tubercle bacillus some place we happened to miss. The result of this was a relatively pure tuberculosis in animals which had not been previously exposed to it.

Dr. Fisher: Dr. Blalock.

Dr. Blalock: Dr. Fisher, I arise in the main to express thanks and gratitude to Dr. Olson. When Dr. Scott first talked to me abut this problem, it became obvious that we did not have the facilities in the Department of Surgery to carry out work on experimental tuberculosis in monkeys. On talking to Dr. Marshall and Dr. Rich and others it was suggested that possibly Dr. Olson of the National Institutes of Health might be interested in a cooperative endeavor. Certainly we are greatly indebted to Dr. Olson and his group not only for providing facilities but also for much of the planning and execution of the experiments.

This study which has been reported by Dr. Scott is an important one. I am sure that Dr. Olson and Dr. Scott and Dr. Hanlon will be the first to admit that there are many unanswered problems. For example, they would like to know how much blood is going through each lung and through each lobe of each lung.

I hope Dr. Scott, in closing, will develop the original hypothesis that was proposed by Dr. William Dock of Brooklyn as to the reasons that the upper lobe of the lung of the human is particularly apt to be affected in tuberculosis. Do the observations on monkeys throw any light on this point?

Dr. Scott has stated that no clinical applications are apparent thus far as a result of their work but this is frequently the case in the early stages of any problem. Let us recall the work of Dr. George Whipple on experimental anemia which led subsequently to the use of liver by Minot and Murphy in the treatment of pernicious anemia, and also of the early work of Fleming which played a part in the subsequent

development of penicillin by Florey and his group. In brief, I think that the observations that have been reported by Dr. Scott are extremely interesting.

Dr. Fisher: Are there any other expressions?

Dr. Lilienthal: I wonder if I could induce Dr. Scott or Dr. Olson to speculate a little further on the mechanism of the effects of arterialization that they have shown so beautifully in these elegant experiments. Arterialization, no matter whether produced by introduction of the systemic-pulmonary anastomosis or by pulmonary artery ligation resulted in caseation. I wonder whether they would speculate on what factors might be involved.

Dr. Fisher: I think this brings up an interesting point, because if we can say that a difference in oxygen saturation has been produced in these areas, this gives some support to the results that Dr. Rich and Dr. Follis, and other workers in different clinics have obtained with animals and *in vitro*. They have shown that a low oxygen tension will produce a very slow growth of the tubercle bacillus in the test tube and will inhibit the lesions of the tuberculosis in animals. There has to be a fairly low oxygen saturation to do it. This report may be a corollary to that work. In the treatment of any sort of infection we have to think always not only of factors that will favor the cells of the host and hinder the growth of the bacteria, but have to think also what factors may be beneficial to the bacteria themselves.

This may be of very practical importance, because there are different situations when patients with tuberculosis are subjected to various oxygen tensions, and tissues may be saturated with various degrees of oxygen, and we want to know whether or not the sort of reaction described by Dr. Scott will occur in patients.

On the other hand, where patients are benefited by collapse of the lung, it has been speculated that because the blood supply is decreased and the oxygen saturation lowered, we may have one of the reasons at least for the beneficial effects of collapse therapy. Now, in patients who have tuberculosis, and are exposed to high oxygen as a therapeutic measure, this might exert a detrimental effect. Probably the time factor is the important thing, and it may be necessary to keep that exposure up longer than is actually carried out in the majority of cases. I would like to ask Dr. Scott if he has any information in this regard which might throw any light on that phase of the problem.

Dr. Scott: Dr. Fisher, if I could start with Dr. Blalock's question in regard to Dr. Dock's original hypothesis and what bearing this group of experiments of ours has on it. In the beginning we thought that if Dr. Dock were right, and if the apical localization of tuberculosis were indeed related to inadequate arterial blood flow through the apex, an end-to-side type of anastomosis, with the increment of flow from the systemic artery superimposed on existing pulmonary flow, would greatly increase the blood flow to the lungs and might possibly improve tuberculosis; that is to say, the procedure might inhibit the course or the extent of the

disease, if Dock's hypothesis were correct. You have seen the results of the experiments.

In regard to a question which has been raised in the past—does the disease get worse? Is caseous tuberculosis as you have seen it demonstrated in these experiments worse than closely packed miliary disease? That question was raised by Dr Ravitch some time ago. We asked Dr. Rich what he thought—which is worse—diffuse caseous disease or diffuse miliary lesions? He told us that there was no question about the fact that the diffuse caseous process is much more severe and is much worse, as far as the animal is concerned, than is miliary disease.

In answer to Dr. Lilienthal's question, I think we can only speculate about the hemodynamic factors. In our initial experiments when we did end-to-end anastomosis between systemic and pulmonary arteries and observed these caseous changes in the lung, we considered four factors which might be of significance. One is the blood flow to the lung. Under the conditions of an end-to-end anastomosis at the present time no one knows what the relative partitions of blood flow are between the two lungs in normal animals without tuberculosis. We hope to carry out some work on this and, when an overdue galvanometer comes, perhaps we can.

Another possible factor is a change in arterial pressure. Dr. Blalock, Dr. Levy, and others have found that just a few millimeters distal to an end-to-side or end-to-end systemic-pulmonary anastomosis the arterial pressure is not greatly elevated. As a matter of fact, at a very short distance from the anastomosis the pulmonary arterial pressure drops to normal levels. It seems most unlikely that change in pressure would be the factor here.

The third factor which we considered was the possibility of a focal recirculation of tubercle bacilli in the bacteremic phase of the disease toward the termination of life of the animal. Organisms discharged into the blood stream from extra-pulmonary lesions should come back to the lung on the side contralateral to the end-to-end anastomosis. As far as the intra-pulmonary lesions go, there is certainly a set-up in which a vicious cycle may operate. From lesions in the lung on the side of the anastomosis, organisms may be discharged into the pulmonary veins, go on to the left heart and back through the anastomosis to reseed that lung. That is a real possibility in an end-to-end anastomosis. However, we feel that the experiments done with pulmonary artery ligation probably negate reseeding as the hemodynamic factor, if the same common denominator is working in the two sets of experiments. Certainly, when the pulmonary artery is ligated reseeding via bronchial arteries must be totally different yet the end result in the two experiments was the same.

We have felt that increased oxygen tension probably is the most likely factor. Of the four things that came to our minds, increased oxygen tension in the blood perfusing the lung is the one factor common to these two sets of experiments. We are not in a position, Dr. Fisher, to say more about the effect of oxygen. Does the bacillus gets its oxygen from the blood perfusing the lung or from alveolar air directly? Perhaps Dr. Riley could help us with that.

Dr. Fisher: Dr. Riley, do you want to say anything about it?

Dr. Riley: Simply that the level of oxygen in the alveoli is a function of both the ventilation and the blood flow. It seems to me that the relationship between ventilation and blood flow has been varied in these studies in such ways as to make the oxygen tension higher in the areas which subsequently developed more caseous tuberculosis. As to the quantitative aspect, there is not enough information to judge from. I think these are absolutely beautiful experiments. What may come from them is hard to predict, but I suspect a great deal.

Dr. Fisher: The second paper will actually be a moving picture entitled

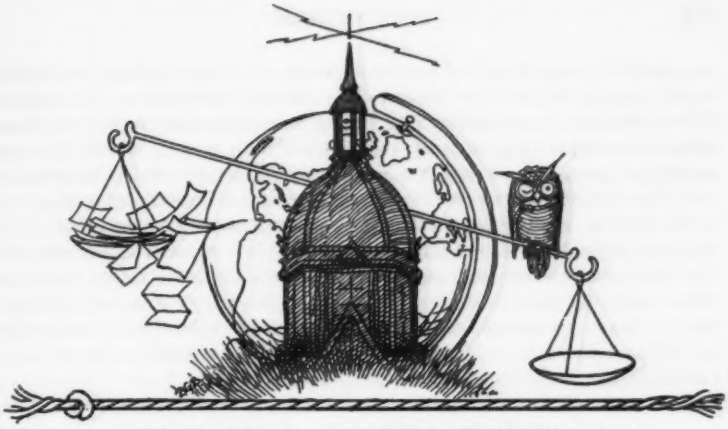
EMBRYOLOGY OF THE EYE

and is presented to us through the courtesy of Dr. A. C. Woods and Dr. G. W. Corner. (Making of the picture was explained and due credit given to those responsible for it. Motion picture shown).

Dr. Fisher: Does anybody want to add anything to this? Dr. Friedenwald? Dr. Grafflin?

Dr. Grafflin: Only a hearty "well done."

Dr. Fisher: I wish to thank the speakers, and call the meeting adjourned.



BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of the Bulletin)

Brain and Behavior. By N. E. ISCHLONDSKY. 182 pp. $7.00. *The C. V. Mosby Co., St. Louis, Missouri.*

The title of this book—probably a concession of the author to the publishers for the sake of making it popular—should be "Pavlovian Induction." The subtitle gives the description of the contents: "Induction as a Fundamental Mechanism of Neuro-Psychic Activity. An Experimental and Clinical Study with Consideration of Educational, Mental-hygienic and General Sociological Implications." This book attempts to extend Pavlov's concepts of induction by experiments and explanations to both clinical and everyday human examples. The author is one of the best informed of those who have attempted to present clearly Pavlov's concepts and to extend these concepts to clinical material. Ischlondsky has made a great service through his publication "Neuropsyche und Hirnrunde," Vienna, 1930. He understands probably as well or better than any living psychiatrist the Pavlovian work and concepts. From time to time he has extended these by his own clinical experiments.

The present book is a rather charming monograph on induction. It begins with the first use of the term by Hering with color induction, and traces its subsequent adoptions by Sherrington and by Pavlov. The body of the book is concerned with the author's own experiments in the human being, and his theoretical explanations of the results. He explains on the basis of induction some of the phenomena dealt with by Freud—love and hatred, slips of the tongue, ambivalence, hysteria. Clinical cases are used as examples.

The book is clearly written and the material easily accessible to any educated

person. It will perhaps make a greater appeal to the general medical reader than to the indoctrinated specialist. In spite of its admirable traits it is not free from the difficulties which the application of laboratory principles to human life faces. These difficulties are those that beset any of us who attempt to apply widely principles established in another setting. A science of human nature will not be adequate until that time when we are able to predict on the basis of known laws—rather than of the *post hoc* explanation of what has already happened by reference to the supposed principles. But owing to many complex factors—such as are operative in causing the weather—both psychology and psychiatry have a long way to go before achieving this result. Nevertheless it is encouraging that even for short periods we are able to make certain predictions by the application of the principle of induction. The clear, bold and scholarly trial which Ischlondsky records in this book should be a contribution in this complex field.

HORSLEY GANTT

Secretory Mechanism of the Digestive Glands, 2nd edition. By B. P. BABKIN. 1027 pp. $20.00. *Paul B. Hoeber, New York.*

It is evident that Dr. Babkin has put much study, much thought, and much tender care into this book which deals with a field to which he has contributed so competently. In it he analyzes and, to a degree, draws conclusions from approximately 2000 published reports dealing with the morphology, physiology, physiopharmacology and biochemistry of the glands of the digestive system. The volume is replete with illustrations, graphs, and tables, nearly a half reproduced from reports made by himself and his associates. The task of compiling and interpreting this large quantity of often conflicting data has apparently been motivated by the desire of the author to understand the structure and function of the cells responsible for the finished products, the physiological reactions that guide and contribute to that end, and the biochemic reactions that produce the several digestive secretions. The book does not treat with the effects of digestive secretions on food or absorption from the lumen of the bowel.

The volume may be regarded as a valuable source of reference; within its thirty chapters are details of experiments, and descriptions of the techniques utilized. This is particularly the case when the author relates his investigations and those of his associates. His extensive reading, his wide experience, and academic interest often lead him to include data of only historic interest. An example of this tendency may be seen in his review of secretin which occupies twenty pages. It opens with the sentence "It took several decades to prove conclusively that a solution of hydrochloric acid, when introduced into the duodenum, stimulates pancreatic secretion humorally by releasing secretin from the intestinal mucosa." The author was apparently often in a quandary deciding whether to include reviews of investigations for historical interest or not refer to them in the interest of conciseness.

There is an extensive review of the studies on the autonomic nervous system innervations of the gastric and salivary glands. The author calls attention to the

failure of histologic study to demonstrate the nervous supply of the gastric glands in particular, and stresses the need of correlating histologic findings with physiologic phenomena produced experimentally; especially in terms of adrenergic and cholinergic nerve fibers. He cites the unsatisfactory results obtained using choline or acetylcholine to stimulate gastric secretion, but does not discuss the possible importance of cholinesterase in this regard.

His treatment of gastric mucin and mucoprotein is full and he is impressed with the importance of the latter in protecting pepsin from destruction by hydrochloric acid, and the probable importance of the mucoitin-sulphuric acid of mucus in inhibiting the action of hydrochloric acid. The general subject of gastric secretion, its composition, and the various neurogenic, chemical, humoral factors which effect it are described in nine chapters. Full reviews of eleven individual theories on the variations of gastric acidity are followed by a "modern conception of the regulation of gastric acidity" by the author, who disclaims the idea that his must be final.

His discussion of the pathogenesis of ulcer is purposefully limited but entertaining. Although he specifically states that he has never claimed that hydrochloric acid or vasoconstriction is the sole cause of a peptic ulcer, he is interested in the relation of hydrochloric acid to ulcer formation. He asserts that histamine stimulates the parietal cells to secrete hydrochloric acid and that any pepsin contained in that juice represents the amount of the enzyme contained with the lumen of the gastric glands. He acknowledges that this conclusion is not in accord with those of other investigators he mentions. However, the evidence he presents gives strong support to his conclusions. The author asserts that pepsin is secreted as the result of vagal stimulation or during the chemical or hormonal phase of gastric secretion when it is accompanied by a strong secretion of hydrochloric acid and minerals. Acetylcholine he considers to be the connecting link in this separation of reactions. He postulates that vagal stimulation releases acetylcholine, the action of which liberates histamine from the gastric glands. This compound then stimulates the parietal cells to secrete hydrochloric acid. He theorizes that some disturbance in the gastric gland may release increased amounts of histamine which in turn would stimulate the parietal cells to excessive formation of hydrochloric acid to participate in the formation of a peptic ulcer. He mentions the suggestions of others that acetylcholine, which has been noted in gastric secretion, has an influence in the production of peptic ulcers by producing local vasoconstriction, theorizing the relative ischemia as a factor in the formation of peptic ulcer. He does not agree that this occurs, but supposing that it does, he sees no conflict between these two suggestions, indicating their actions as complementary. He does not stress the more accepted conclusion that vasoconstrictor nerves are adrenergic and probably elements of the sympathetic component of the automonic nervous system. Does one have to postulate the additional presence of cholinergic vasoconstrictor nerve terminals?

His fulsome review of reports dealing with the morphology and physiology of the salivary glands permit the reader to agree with his opening statement "These

studies will lead us invariably to the conclusion that the supposed double parasympathetic and sympathetic innervation of each secretory cell is extremely doubtful." The reviewer has long thought that the theory of antagonistic autonomic nervous system action was unnecessarily complicated.

One searching for information on the relation of pyloric mucous membrane to the so-called second or chemical or hormonal phase of gastric secretion will find a large amount of data, most of it contradictory. He will probably agree with the author that there is a substance extractable from the antral mucous membrane which causes a secretion of gastric juice following its injection into the animal. Whether it is gastrin, or histamine, or some other substance, he will not discover. More importantly, he will be unable to determine whether the mucous membrane of the pyloric portion of the stomach is essential for prolonged secretion of gastric juice. This may be of interest to those who state that the removal of that portion of the stomach is essential in the surgical treatment of gastric or duodenal ulcer.

The reader is left with the assurance that the published data, while interesting, leaves unsolved the explanations of the many fundamental problems of digestive secretions. The format is impressive, the paper good, and the printing excellent. As is too often the case, the volume is too heavy to hold comfortably while reading.

Much of the ignoble pleasure of jotting contradictory marginalia was lost to the reviewer because of the realization that his old friend would not be there to make his tolerant, pointed, and accurate retorts.

L. M.

Textbook of Endocrinology. Edited by ROBERT H. WILLIAMS, with the collaboration of P. H. FORSHAM, H. B. FRIEDGOOD, J. E. HOWARD, E. J. KEPLER, W. LOCKE, L. H. NEWBURGH, E. C. REIFENSTEIN JR., W. W. SCOTT, G. V. S. SMITH, G. W. THORN, AND L. WILKINS. 793 pp. $10.00. *W. B. Saunders Co., Philadelphia, Pa.*

This is the first edition of a book which fulfils a need long felt in medicine—a text written by outstanding clinicians who are authorities in endocrinology. Advances in this field of medicine have been extremely rapid in the last few decades; this volume brings the reader up to date on the experimental background as well as the clinical application of these discoveries.

The general principles of endocrinology are effectively set forth in the first chapter, including *laws of endocrinology*. The reader might find fault with some of these laws, however, because they are not general enough. It is stated, for example, that "when the amount of hormone produced by the target gland is distinctly less than is required by the body, there is an increased elaboration of the tropic (pituitary) hormone, leading to hyperplasia and hypertrophy of the target gland. This hyperplasia and hypertrophy obviously cannot occur if the target gland is atrophic, as in primary myxedema or in the menopause.

Each known endocrine gland is discussed in a separate section; with one exception, all these chapters are concisely and clearly written. The Ovaries (Chapter 6), however, is unnecessarily long and difficult to read, leaving one more confused than enlightened. In discussing amenorrhea on p. 395, the author states that the

FSH and 17-ketosteroid assays of the urine are still research procedures and rarely indicated, whereas these tests actually are well standardized procedures of definite diagnostic value.

There are excellent sections on the influences of the endocrines on growth and development, and on the as-yet-little-understood neurogenic and psychogenic factors in endocrine dysfunction. Obesity is thoroughly discussed in another chapter, emphasizing again that obesity is not an endocrine disorder. The last section outlines the laboratory procedures which have not been covered in the previous sections and is rather brief; but adequate references are given for those who are interested in the details of the tests.

Noteworthy by its absence is any mention of hyperinsulinism and there is no discussion of the differential diagnosis of hypoglycemia. A section on the breast (both male and female) would be a valuable addition to the book. This was apparently planned, because on p. 222 the statement is made that "the differential diagnosis of gynecomastia is discussed elsewhere in this volume."

The text in general is clearly written, easily read, adequately illustrated, and well indexed. There is a good bibliography at the end of each chapter. Only a few errors in printing occur. On p. 581, in discussing the diagnosis of hypoparathyroidism, symptoms of the acute state are confused with those of the chronic. On the next page, it is stated in the text that tetany following excessive vomiting is accompanied by a decrease in the CO_2 combining power of the serum, whereas in Table 42 on the same page, the increased CO_2 combining power that occurs is correctly tabulated.

On the whole, this new book is a valuable addition to the physician's library.

H. F. K., Jr.

Textbook of Abnormal Psychology, 4th edition. By Roy M. Dorcus and G. Wilson Shaffer. 717 pp. $5.00. *Williams & Wilkins., Baltimore, Md.*

The fourth edition of one of the most successful advanced texts on abnormal psychology has been brought up to date by conscientious inclusion of recent developments, the revision of the material on disorders due to brain damage, and by the addition of an appropriate chapter on psychosomatic disturbances. The sound approach of offering meaning to dysfunction as aberration from the range of normal is continued. The approach, however, is through exposition of the physiologic and psychologic basis for various aspects of human functioning rather than through offering an understanding of the acquisition of socialized behavior by the biologically endowed organism. The behavioral development of the child receives rather scant attention, and reference to Gesell's work is absent. Similarly, ethnologic basis for comparison of behavior is not considered, and the work of Margaret Mead, Benedict, Kluckhohn, and other anthropologists who have greatly enriched psychology is not included. As the book is primarily intended for advanced students of psychology, the rather brief treatment of projective techniques, their rationale and meaning to experimental psychology, constitutes a definite shortcoming.

T. L.

Differential Diagnosis of Internal Diseases. Clinical Analysis and Synthesis of Symptoms and Signs. By JULIUS BAUER. 866 pp. $12.00. *Grune & Stratton, New York.*

This book includes a small note by the publisher stating there has been minimal editorial change of the original manuscript. The book shows it. The material is divided into two parts: Part One—Leading Symptoms and Part Two—Leading Signs. As an example of the lack of significance of such divisions a few of the chapter headings in Part One are: Chapter 9—Paralysis, Incoordination and Involuntary Movements; Chapter 12—Hemorrhages; and in Part Two are: Chapter 14—Hyperthermia, Fever and Infectious Diseases; Chapter 18—Hemopoietic System and Chapter 20—Glycosuria.

A few of the author's statements on headache are cited here as illustrations of the level of clinical thinking employed. A possible inciting factor suggested in the mechanism of migraine is "autonomic nervous inbalance with neuropathic constitution." A treatment for migraine that is recommended is "desensitization" with small amounts of histamine because "such desensitization is meant as a kind of accustoming rather than as an antiallergic, immunologic procedure." An explanation offered for headache in patients with erythremia is "the viscosity of the circulating blood or thromboses of smaller or larger cerebral vessels."

Despite the title of the book much space is devoted to discussion and speculation on pathogenesis of various diseases. "The common peptic ulcer of younger persons develops on the predisposing bases of a constitutional (hereditary) biologic inferiority of the gastrointestinal tract in general and of the stomach and duodenum in particular." "Constitutional biologic inferiority" and "neuropathic" are recurrent descriptive terms used in explanations of many diseases.

Useless eponyms are scattered profusely throughout the book. Numerous case histories are presented in which the diagnosis is not clearly established but are cited as examples of whatever disease entity the author happens to be discussing.

The incorrect statement is made in Chapter 3 that "Intussusception and internal strangulation fail to show general abdominal distention." Another error is "Malignant pheochromocytomas do not cause paroxysmal hypertension." On page 138 the author states "Cultures from the synovial fluid of gonococcic arthritis yield positive results in the majority of the cases," but on page 470 he writes "In gonoccic arthritis the organisms can be cultured from the joint fluid in only about 25 per cent of the cases."

In Chapter 12 on "Hemorrhages" hemophilia is not discussed.

Repeated tuberculin tests are recommended for their prognostic value in following cases of tuberculosis.

"The blood chloride has been found diminished in acute mercury poisoning" and without mentioning the possible effect of early vomiting the author concludes the chlorides "obviously must be retained in the tissues." Elsewhere he states "the blood NaCl" may become concentrated in other conditions.

The following unqualified assertions are unproven. In discussing porphyria he states "The liver plays an important role in the pathogenesis of the disease."

"Nucleic acid derivatives (pentnucleotide) act probably as stimulus for leukocyte production." "Functional irritation of the autonomic system" is the explanation for precomatose diabetic abdominal pain. "Hyperactive spleen impairs the activity of bone marrow by its hormone." The meteorism that may precede ascites in patients with portal hypertension "is caused by insufficient absorption of intestinal gases by the circulating blood." "In the etiology of leukemia a constitutional (genetic) factor plays an important role." "Depletion of glycogen is the main biochemical aspect of hepatic insufficiency." And in discussing idiopathic thrombocytopenia "it must be inferred that the abnormal gene or gene complex extends its action upon both the production of thrombocytes and the capillaries." The cutaneous atrophy and pigmentation found in some patients with rheumatoid arthritis "is caused rather by an alteration of the sympathetic nervous system." "It appears that the anti-anemic principle of the liver releases the potent folic acid from its conjugates." The cause for leukopenia in severe infection is "due to exhaustion of the bone marrow."

This book is *not* recommended. Although there are interesting statements made and unusual observations reported their reliability is open to question in light of the inaccuracies and lack of critique revealed in the above quotations.

P. F. W.

A Text-Book of X-ray Diagnosis, 2nd edition. By British Authors in Four Volumes. Vol. 3. Edited by S. COCHRANE SHANKS and PETER KERLEY. 830 pp. $18.00. *W. B. Saunders Co., Philadelphia, Pa.*

This review is of Volume III which is the second book to be released following Volume IV. This last volume was reviewed in the December 1950 issue of The Bulletin of The Johns Hopkins Hospital. Volume III concerns the abdomen.

On the frontispiece is a short quotation of Sir James Mackenzie Davidson, who wrote in Quain's Dictionary of Medicine, third edition, 1902 "The abdomen is very difficult to examine by X-rays. With the exception of gaseous distention of the stomach, renal calculi, and metallic foreign bodies, which can be detected, little information can be obtained." It is an interesting commentary that within a period of 48 years diagnostic radiology has advanced to such a degree that a valuable and succinct 830 page book has been written dealing with the abdomen alone.

This volume is divided into six parts as follows: 1—Alimentary Tract, 2—Biliary Tract, 3—The Abdomen, 4—Radiology in Obstetrics, 5—Gynaecological Radiology, 6—Urinary Tract. These subjects are thoroughly discussed and well illustrated by seven of the seventeen eminent British authorities contributing to the entire work. After each part is appended a valuable subject reference.

In comparison with the previous edition there has been much basic revision, expansion, and modernization. Part I, The Alimentary Tract, has been rewritten, by S. Cochrane Shanks. A. S. Johnstone, and Cecil G. Teall. Particularly praiseworthy are the sections on the esophagus, the stomach and duodenum after operation, and the diaphragm. An entirely new section on the alimentary tract of infants and children has been added.

Part 2, The Biliary Tract by Peter Kerley, has remained essentially the same and is still a scholarly review of the subject.

In Part 3, The Liver, Spleen, Adrenals, and Pancreas, S. Cochrane Shanks has expanded the chapter devoted to the adrenals, and especially the pancreas, an organ which has been the bane of many radiologists. Lesser changes have been made in the discussion of liver abscesses and carcinoma.

Part 4, Obstetrics by E. Rohan Williams, is entirely new, very complete, and excellently done. A departure is made from the British authorship in that several outstanding American authors have contributed short chapters on specific pelvimetry techniques.

Part 5, Gynaecological Radiology also by E. Rohan Williams, has undergone complete transformation. It has been rewritten, enlarged, and modernized. The problems of hysterosalpingography are clarified considerably.

Part 6, Urinary Tract, was revised by S. Cochrane Shanks and A. S. Johnstone. Although little has been added, the organization of the material has been much improved.

Again it should be noted that the reversed tonal scale in the reproduction of roentgenograms is objectionable to the average American reader. The reviewer has heard numerous comments from his colleagues that the superb text is in no way enhanced by the reversed reproductions. The reviewer wonders whether British and Continental European medical writers prefer to use reverse reproductions or do so for technical reasons. Notwithstanding Volume III is highly recommended as an outstanding and even monumental reference text of x-ray diagnosis of diseases related to abdominal organs and adjacent structures.

D. M. G.

Intestinal Intubation. By MEYER O. CANTOR. 333 pp. $7.50. *Charles C. Thomas, Springfield, Illinois.*

The ubiquity of the long intestinal decompression tube in all fields of medicine today where derangements of bowel physiology are encountered has undoubtedly created a demand for a reference which would serve at once as working manual and source book of related data. Dr. Cantor's monograph attempts to satisfy this demand and on the whole achieves its purpose.

The presentation leads the reader through an engrossing historical review to a discussion of the anatomical and physiological factors involved in intestinal distention and intubation. The author then describes in detail the technique of intubation with particular reference to his own decompression tube. Succeeding chapters discuss intubation in specific clinical conditions, types of suction, and the role of the roentgenologist. Two concluding chapters concern experimental observations on the effect of intestinal gases on balloons.

The monograph presents an excellent set of data on techniques and broad experiences with intestinal decompression tubes, and as such provides a valuable reference which will save many hours of clinical trial and error. The sole criticism would be leveled at the literary style which is so discursive as to be distracting in

places, and secondly at the reiteration (perhaps pardonable) of the virtues and advantages of the author's "simplified intestinal decompression tube."

J. C. H.

Bronchoesophagology. By CHEVALIER JACKSON and CHEVALIER L. JACKSON. 366 pp. $12.50. *W. B. Saunders Co., Philadelphia, Pa.*

This latest in the series of books by the Jacksons on bronchoesophogology and laryngology maintains the high standard set by their previous texts.

There are a great number of illustrations (most of them excellent). The descriptions of techniques are both thorough and brilliantly clear.

The book is chiefly open to criticism because of the relatively small space allotted to the use of bronchoscopy in pulmonary diseases not associated with foreign bodies. Of the 225 pages devoted to "Bronchology" only 70 pages are included in the chapter on "Obstructive Conditions of the Bronchial Tree." There seem to be less than 4 pages devoted to the bronchoscopic problems connected with pulmonary tuberculosis.

In spite of this drawback it is a text which is of considerable interest and should be of great use to the student attempting to master the technique of per-oral endoscopy.

D. F. P.

Grundlagen der Gynäkologie. Funktionelle Anatomie, Regulationsvorrichtungen Untersuchungstechnik. By HEINRICH MARTIUS. 144 pp. Ganzleinen DM 23.40 ($5.55). *Georg Thieme Verlag, Stuttgart.*

From the title of this little book, one might expect it to be a synopsis of gynecology, but it is not. In his preface the author designates it as a "propadeutik" of this special field, by which, for the benefit of those who do not have a dictionary handy, he means an introduction to certain basic subjects as a preparation for the study of gynecology. The book is therefore divided into three sections, viz. (1) anatomy, though the author emphasizes that he has in mind "functional anatomy"; (2) the regulatory mechanism of the female sex organs, including especially the endocrines; and (3) the methods and technic of gynecological examinations. Ordinarily these subjects are included in textbooks of gynecology, and it is of interest to learn why a separate volume was devoted to them.

Martius is the distinguished director of the Göttingen Frauenklinik, and the author of four well-known textbooks, all excellent, one on Obstetrics, one on Gynecology, one on Operative Obstetrics, and one on Operative Gynecology. He explains that while such basic subjects as those embraced in the present volume can not be excluded from a textbook of obstetrics, he preferred to make his gynecologic textbook purely clinical, and to prepare this separate "propadeutik" for future gynecologists. Whatever one's reaction may be to this reasoning, and that of the gynecologist may differ from that of the obstetrician, all will agree as to the excellence of the content of this small volume of 130 pages, enriched as the text is with no less than 113 superb illustrations, many of them being beautifully exe-

cuted color drawings. A large proportion of the illustrations are of schematic or semi-schematic type, but they carry a more powerful teaching punch than would pictures emphasizing only exact verisimilitude. The artist, Käthe Droysen, deserves as much credit as the author.

The book is printed on high grade paper and its general format is excellent. A fairly complete list of references is offered. A pleasant novelty is the use of footnote comments on some of the authors mentioned in the text. For example, one of these reads, "Herman Treschow Gartner, Danish anatomist 1795–1827. Found Gartner's duct, 1822, in the cow. It was later discovered in the human." Again, "Ludwig Fraenkel, gynecologist, formerly in Breslau, now in Montivideo, born 1870."

For what it purports to be, this small volume can be highly recommended. Even the specialists, including those who do not read German, will profit greatly from the remarkably good illustrations which, to my mind, constitute the greatest asset of this book.

EMIL NOVAK

Psychosomatic Medicine. Its Principles and Applications. By FRANZ ALEXANDER, (with a chapter on **The Functions of the Sexual Apparatus and Their Disturbances,** by THERESE BENEDEK). 300 pp. $4.00. *W. W. Norton & Co., New York.*

A book by Dr. Alexander on psychosomatic medicine is of necessity an important publication. He has been an outstanding contributor to both the theoretical and clinical aspects of the effect of emotions on medical illness. His interest and his position have led to the many studies of the Chicago Psychoanalytic group upon psychosomatic conditions. The volume lives up to expectation in many respects.

Dr. Alexander does not attempt to deal with the subject matter that might be covered by the term "psychosomatic medicine" in anything resembling an exhaustive manner. To a considerable degree he has limited himself to topics in which he has had a personal interest. The first section of the book gives a resume of Dr. Alexander's concepts of the field of psychosomatic medicine. It is a coherent expression of a holistic approach with over-emphasis on the importance of psychoanalysis in reorienting the philosophy of medicine. It does not seem to do justice to the consequences of the trend of American thought as expressed by James and Dewey and integrated into medicine by Adolf Meyer. The author's theoretical considerations concerning the means by which emotions influence physiologic activity are thought provoking leads into future studies. The second part of the book which deals with emotional factors in different diseases is especially noteworthy for the brief statements of significant matter. Unfortunately this section of the book is too brief to do justice to certain diseases, and for the most part the illustrations of case material are presented in cursory fashion. The reader gains the impression that this portion of the book was written rather hastily, but the chapters dealing with the illnesses that the author has investigated himself are well done.

A lengthy chapter on sexual functions and their disturbances contributed by Therese Benedek appears totally inappropriate to this volume. Although it contains considerable excellent material, its orientation in more classical analytic theory and its use of psychoanalytic terminology, requires considerable foundation in analytic theory from the reader, which fortunately is not true of the remainder of the book. The final chapter on therapy is too brief to be of any real value, and it seems to the reviewer to be unfortunate that the author who has given so much consideration to therapy and to useful modifications of psychoanalytic therapy has not gone beyond broad generalizations in his discussion of therapeutic maneuvers.

The book is important. It will be useful in teaching undergraduate and graduate students in both medicine and psychiatry. However, it is naturally a disappointment to those who work in this field that Dr. Alexander has not chosen to write a more comprehensive book.

T. L.

BOOKS RECEIVED FOR REVIEW

Biological Antioxidants. Transactions of the Fourth Conference, December 8–9, 1949. Edited by COSMO G. MACKENZIE. Associate Editors, E. V. JENSEN AND RALPH T. HOLMAN. 181 pp. $3.25. *Josiah Macy, Jr. Foundation, New York.*

Blood Clotting and Allied Problems. Transactions of the Third Conference, January 23–24, 1950. Edited by JOSEPH E. FLYNN. 224 pp. $3.00. *Josiah Macy, Jr. Foundation, New York.*

The Collected Papers of Adolf Meyer. Four Volume Set $30.00. Edited by EUNICE WINTERS. Vol. 1, Neurology, Special Editor, LOUIS HAUSMAN. 693 pp. *The Johns Hopkins Press, Baltimore, Md.*

Exotische Krankheiten und Krankheitsverläufe. By F. O. HÖRING. 407 pp. Ganzleinen DM 36. ($8.55). *Georg Thieme Verlag, Stuttgart.*

Family Centered Maternity and Infant Care. Supplement I to Problems of Infancy and Childhood. Transactions of the Fourth Conference, 1950. Edited by EDITH B. JACKSON AND GENEVIEVE TRAINHAM, with the Assistance of Members of the Rooming-In Committee. 29 pp. 25 cents. *Josiah Macy, Jr. Foundation, New York.*

Functional Anatomy of the Limbs and Back. A Text for Students of Physical Therapy and Others Interested in the Locomotor Apparatus. By W. HENRY HOLLINSHEAD. 341 pp. $6.00. *W. B. Saunders Co., Philadelphia, Pa.*

Fundamentals of Clinical Fluoroscopy: With Essentials of Roentgen Interpretation. By CHARLES B. STORCH. 196 pp. $6.75. *Grune & Stratton, Inc., New York.*

Histamine Antagonists, Review No. 3, Chemical-Biological Coordination Center. By FREDERICK LEONARD AND CHARLES P. HUTTRER. 122 pp. $1.50. *National Research Council, Washington, D. C.*

The Low Fat, Low Cholesterol Diet. By E. VIRGINIA DOBBIN, HELEN F. HOFMAN, HELEN C. JONES, LENORE LYON AND CLARA-BETH YOUNG. Introduction by THOMAS P. LYON AND JOHN W. GOFMAN. 371 pp. $3.45. *Doubleday & Co., Inc. New York.*

Metabolic Interrelations. Transactions of the Second Conference, January 9–10, 1950. Edited by EDWARD C. REIFENSTEIN, JR. 279 pp. $3.95. *Josiah Macy, Jr. Foundation, New York.*

Pharmacology, 2nd edition. Oxford Medical Outline Series. By MICHAEL G. MULINOS. With a Foreword by CHARLES C. LIEB. 484 pp. $5.00. *Oxford University Press, New York.*

Physical Diagnosis, 4th edition. By RALPH H. MAJOR. 446 pp. $6.50. *W. B. Saunders Co., Philadelphia, Pa.*

Physiology of Shock. By CARL J. WIGGERS. 459 pp. $5.00. *The Commonwealth Fund, Division of Publications, New York.*

Psychotherapy. By PAUL SCHILDER. Enlarged and Revised Edition arranged by LAURETTA BENDER. 396 pp. $5.00. *W. W. Norton & Co., Inc. Scranton, Pa.*

Your Prostate Gland. Letters from a Surgeon to His Father. By REED M. NESBIT. 50 pp. $2.00. *Charles C. Thomas, Springfield, Illinois.*

Symposium on the Healthy Personality. Supplement II: Problems of Infancy and Childhood. Transactions of the Fourth Conference, March, 1950. Edited by MILTON J. E. SENN. 298 pp. $2.50. *Josiah Macy, Jr. Foundation, New York.*

Trephine Technique of Bone Marrow Infusions and Tissue Biopsies, 4th edition. By HENRY TURKEL. 60 pp. $1.00. *Gale Printing Co., Detroit, Michigan.*